



Usage of metformin in patients with type 2 diabetes mellitus

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Abstract

Metformin is an old drug which is widely prescribed for the treatment of type 2 diabetes mellitus (T2DM). It is recommended as the first line oral anti-hyperglycaemic agent in Australia, United States and most European countries. It reduces haemoglobin A1c (HbA1c) by 10-20 mmol/mol (approximately 1-2%), and does not cause weight gain or hypoglycaemia. Metformin is well tolerated in most patients and has potential clinical advantages in patients with cardiovascular disease. The clinical conundrum facing practitioners while prescribing metformin is the potential risk of lactic acidosis, which although rare is often fatal. The current official product information recommends that metformin should be avoided or the dosages adjusted in patients with coexisting conditions that are likely to increase the risk of lactic acidosis. The safe use of metformin is still under debate, which may confuse practitioners when prescribing. Thus we aimed to provide more evidence regarding the current prescribing pattern and usage of metformin in Australia, and to explore the safety of metformin, especially its association with lactic acidosis.

To achieve this aim, a number of complementary studies were conducted. We evaluated the prescribing pattern of metformin in patients who were admitted to a local hospital. The main finding of this study was that metformin was often being prescribed ‘inappropriately’ with regards to the restrictions listed in the official product information, in terms of usage with contraindications and in higher than recommended dosages. Similar results were observed when we reviewed the use of metformin in patients who lived in the community or aged care facilities receiving either Home Medicines Reviews or Residential Medication Management Reviews respectively. This study included more than 6,000 patients living across Australia. Our findings were consistent with those conducted in other countries.

To evaluate the potential association between the use of metformin and lactic acidosis, we reviewed all the potential adverse drug reaction cases of metformin which were reported to the Therapeutic Goods Administration (TGA) of Australia from 1971 October 2014. A total of 152 potential cases of lactic acidosis associated with metformin were reported to the TGA. Approximately 75% of these cases had at least one clinical condition which itself might cause acidosis. The incidence of metformin-associated lactic acidosis (MALA) was estimated to be 2.3 (95%CI, 1.5-3.1) cases per 100,000 patient-years between 1997 and 2011. This relatively low incidence of MALA may be explained by the nature of spontaneous reports to the TGA. In addition, we reviewed the cases of patients who were admitted to a local hospital with lactic acidosis. Over a four-year period, 139 patients were identified using the digital medical record; only 23 patients had T2DM and 11 patients had been taking metformin.

To further verify the low incidence of lactic acidosis in metformin users, we conducted a literature review on regular tested lactate level among metformin users. Limited studies have reported the lactate levels with continued metformin usage. Few studies reported that the lactate level in metformin users did not alter after the initiation of metformin. However, compared to the lactate level of patients without being treated with metformin, the level in metformin-treated patients was, on average, higher; but, remained within the normal range.

The findings of studies contained in this thesis indicate that it is generally safe to use metformin in most patients with T2DM. Recently, therapeutic guidelines in Australia have modified the prescribing recommendations for metformin, with less restrictions in patients with so-called “contraindications”. It is necessary to update the official product information for metformin, which will give a clearer recommendation to prescribers in practice.

List of Abbreviations

AE	adverse effect
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMH	Australian Medicines Handbook
AMP	adenosine monophosphate
AMPK	adenosine monophosphate-activated protein kinase
ATP	adenosine triphosphate
BMI	body mass index
CG equation	Cockcroft-Gault equation
CHD	coronary heart disease
CKD	chronic kidney disease
CKD-EPI equation	chronic kidney disease-epidemiology collaboration equation
CrCl	creatinine clearance
DM	diabetes mellitus
DPP-4 inhibitor	dipeptidyl peptidase-4 inhibitor
e.g.	for example
eGFR	estimated glomerular filtration rate
ESKD	end stage kidney disease
FDA	Food and Drug Administration (United States)
FDS	Fremantle diabetes study
G6Pase	glucose 6-phosphate
GGT	gamma-glutamyl transferase
HbA1c	haemoglobin A1c
HIV	human immunodeficiency virus
HMR	home medicines review
ICD	International Classification of Diseases
ICPC-2	International Classification for Primary Care-2
LA	lactic acidosis
LKB1	liver kinase B1
MALA	metformin-associated lactic acidosis

mGPD	mitochondrial glycerol phosphate dehydrogenase
MILA	metformin-induced lactic acidosis
NAD	nicotinamide adenine dinucleotide
NRIT	nucleoside reverse transcriptase inhibitor
OCT	organic cation transporter
PCOS	polycystic ovary syndrome
PI	product information
PIP	potential inappropriate prescribing
RHH	Royal Hobart Hospital
RMMR	residential medication management review
SCr	serum creatinine
SD	standard deviation
SPSS	Statistical Package for Social Sciences
$t_{1/2}$	half-life
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TG	Therapeutic Guidelines (Australia)
TGA	Therapeutic Goods Administration (Australia)
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
Vd	volume of distribution
vs.	versus

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Thesis overview

Metformin is widely used in the treatment of type 2 diabetes mellitus (T2DM). The major barrier for practitioners to prescribe metformin is the concern of developing lactic acidosis (LA). The caution may be related to the other biguanide, phenformin, which was used to treat T2DM; this drug was removed from the market due to the association with high incidence of LA. The concerns of LA in metformin-treated patients are under debate, as in comparison to phenformin, the reported incidence of LA in metformin users is much lower.

Limited studies have been conducted in Australia regarding the use of metformin. This thesis, which explores the current usage of metformin in Australia and the LA cases associated with metformin, is divided into five parts.

Part A of this thesis (Chapter 1) includes the background information on: (i) the current facts of T2DM in Australia; (ii) metformin and its clinical usage; and (iii) LA and its potential association with metformin. Diabetes is one of the most common chronic diseases in Australia, with T2DM accounting for approximately 85% of diabetes cases. Chronic kidney disease (CKD) is both a complication and an independent comorbidity of diabetes, which has been estimated to affect approximately 50% of patients with T2DM globally. There are limited medication choices to treat T2DM in patients with CKD effectively; as most of the newer drugs have not been studied in this population. Metformin has been used for more than half a century, provides the best effect in reducing haemoglobin A1c (HbA1c) among all the oral anti-diabetic medications and has evidence in decreasing the risk of diabetic related complications. However, its potential benefits in macro-and microvascular effects may be overlooked due to the concern of LA. The official product information presents a list of contraindications to the use of metformin, including: (i) acute or chronic diseases which may cause tissue hypoxia (i.e. cardiac failure); and (ii) conditions with the potential to alter renal function (i.e. dehydration),

as well as renal dysfunction (creatinine clearance < 60 ml/min). Studies have reported that the incidence of LA in metformin-treated patients is low. According to a Cochrane review, the estimated LA incidence among the patients treated with antidiabetic medications was approximately 4.3 per 100,000 patient-years among metformin users and 5.4 cases in non-metformin users.

Given this background, we aimed to undertake two medication review studies, which explored the prescribing patterns of metformin in patients with T2DM who were admitted to the hospital and those who were living in the community or aged care facilities in Australia (**Part B**, Chapter 2 & 0). The primary objective was to explore the prescribing pattern of metformin in practice, in terms of the use of the drug in the presence of contraindications and/or in excessive dosage based on renal function. The first study (Chapter 2) reviewed a total of 301 patients receiving metformin who were admitted to a local hospital over an 8-month period in 2012. At admission, more than 30% of patients receiving metformin were found to have contraindications to metformin, and more than 20% of patients were prescribed with excessive dosage according to their renal function. The most common contraindications in this study were cardiac failure and liver dysfunction. Four patients were found to have potential LA (defined as lactate > 5.0mmol/L and pH < 7.35); however, all these patients had contraindications to metformin use. The other medication review study (0) pertaining to more than 6,000 patients in Australia revealed that approximately 12% of patients living in the community and 17% of patients living in aged care facilities were receiving metformin inappropriately.

Although we found that metformin was often being used in patients with contraindications to its use or in excessive dosage in decreased renal function, it seems generally safe to use this anti-diabetic medication. **Part C** of this research (Chapter 4 & Chapter 5) evaluated the LA cases reported in metformin-treated patients in Australia. A total of 152 LA cases, which were suspected to have association with the use of metformin, were reported

to the Australian Therapeutic Goods Administration from January 1971 to October 2014 (Chapter 4). More than 25% of patients were reported to have pre-existing contraindications to the use of metformin and approximately 75% had underlying clinical conditions which may have caused acidosis. The incidence of metformin-associated LA (MALA) was estimated to be 2.3 cases per 100,000 patient-years. The study in Chapter 5 was conducted with an intention to collect more detailed medical information on LA in patients receiving metformin who were admitted to the local hospital. Between 2010 and 2013, of the 139 patients admitted with LA, only 23 patients had T2DM and 11 patients had been prescribed with metformin. Based on the findings from two studies in Part C, the incidence of LA in metformin-treated patients in Australia was low and the risk of developing LA may be overemphasised in patients treated with this agent.

To further verify the findings in Part C, a literature review was performed to evaluate the measurement of lactate levels in chronic metformin users (**Part D**, Chapter 6). Limited research has been conducted to monitor the lactate levels in patients treated with metformin. The lactate levels were mostly documented in the case reports of MALA (under acute conditions). Most of the studies included in this review reported that the lactate levels were higher in chronic metformin-treated patients compared to those of non-metformin users, or the levels at baseline (before initiating metformin therapy). However, the lactate levels in metformin users have mostly been reported remaining in the normal range, even in those studies including patients with other underlying clinical conditions.

Part E (Chapter 7) of this thesis presents a general discussion and conclusion of the research.

Part A

Chapter 1 Background

1.1 Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is one of the most prevalent and fastest growing chronic diseases globally and in Australia.¹ T2DM is one of the three main types diabetes mellitus (DM), which also includes type 1 diabetes mellitus (T1DM) and gestational diabetes. DM includes a group of metabolic disorders characterised by hyperglycaemia and abnormalities in carbohydrate, fat and protein metabolism. It is a source of a range of metabolic disturbances which result from inadequate insulin secretion, resistance to the actions of insulin or both. T2DM accounts for approximately 85% of DM cases in Australia, and is usually characterised by the presence of both insulin resistance and relative insulin deficiency.²

1.1.1 Epidemiology

Diabetes currently affects over 415 million adults, and in addition, there are 318 million adults with impaired glucose tolerance.³ It is currently estimated that 1.7 million Australians are living with diabetes and it is thought that half a million of these people are living with undiagnosed T2DM. Furthermore, it is estimated that approximately 280 Australians develop diabetes every day.⁴ Most of the growth in diabetes is due to T2DM, which can be a result of the aging of the population, a reduction in physical activity, the obesity epidemic and decreased mortality in those with diabetes.⁵ Overall, T2DM is much more common in males as compared to females.⁵ Of the 787,500 people reported as having T2DM in 2007-08, 56% of them were males and 44% were females.⁶ Approximately 92% of T2DM patients were 45 years old or more and 45% were 65 years or older.⁶

1.1.2 Burden of disease

According to the latest available data from Australian Institute of Health and Welfare (AIHW), T2DM accounted for a least 60% of DM expenditure in 2009-09. Almost \$1,507 million was spent on DM, which increased by 86% between 2000-01 and 2008-09 while for all disease increased by 60% in the same period. It is estimated that the total cost of diabetes is \$14.6 billion each year in Australia.⁷ Using a conservative estimate, diabetes was projected to be the sixth leading cause of burden of disease and injury in Australia in 2010 (contribution of diabetes to coronary heart disease (CHD) and stroke not included), and responsible for nearly 6.6% of the total disease burden.⁸ T2DM was estimated to account for the great majority (94%) of diabetes burden in 2010, and the ranking of T2DM as a cause of disease burden is projected to increase over time.⁸

1.1.3 Complications of diabetes mellitus

Complications associated with T2DM can arise early in the course of the disease or develop over a number of years. Long-term complications of T2DM include disease of the large blood vessels (macrovascular disease) that can lead to conditions such as CHD, stroke and peripheral vascular disease; and disease of the small blood vessels (microvascular disease) that can cause chronic kidney disease (CKD), nerve damage and retinopathy.⁹ T2DM is the most common cause of severe kidney disease in Australia.⁵

CKD is both a complication of diabetes, and an independent comorbidity presented before diabetes onset. CKD, defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min per 1.73m², is a long-term health condition where a person has kidney damage and/or reduced kidney function lasting for 3 months or more.¹⁰ In addition, both diabetes and CKD are known to be under-reported in the Australian and the global mortality statistics, often being omitted from death certificates as contributory causes of death.^{11, 12} Based on AusDiab

data, more than 90% of the adult diabetes population in Australia with evidence of kidney damage exhibited albuminuria, either alone or in combination with a low estimated eGFR.¹³

Recently, a review regarding the epidemiology of T2DM and associated CKD suggested that CKD was estimated to affect about 50% patients with T2DM globally, and the presence of CKD and its severity markedly influenced disease prognosis.¹⁴ In patients with T2DM, CKD was found to be associated with excess mortality.^{15, 16} T2DM is the single leading cause of ESKD globally, accounting for approximately one-third of all patients initiating renal replacement therapy.¹⁷ As of 2012, the prevalence of DM-ESKD in Australia was 208 per million population.¹³ Together with the population with glomerulonephritis and hypertensive renal disease, the estimated annual incidence of treated DM-ESKD among Australian aged 25 years and older was approximately 1 case per thousand.¹³

1.1.4 Mortality

Globally, approximately 1.5 million deaths were directly caused by DM in 2012.¹⁸ In Australia, a total of 15,095 deaths in 2012 were due to some degree of DM (1 in 10 of all deaths).¹⁹ DM itself is not often the reason directly leading to death, but one of its complications that with be listed as the underlying cause of death.²⁰ The diabetes-related deaths were reported to be 30.9 persons per 100,000 people in 2010 (Figure 1). In Australia, when DM was reported as any cause of death (underlying or associated), the most common contributing causes of death were coronary heart disease (47%), hypertensive diseases (30%), heart failure (21%), kidney failure (21%), and cerebrovascular disease (20%).¹³ T2DM was listed as an underlying or associated cases of death in approximately 50% of all the cases of DM. Males were more likely to die from DM as any cause of death than females, with age-standardised death rates of 78 and 50 per 100,000 population, respectively.²⁰

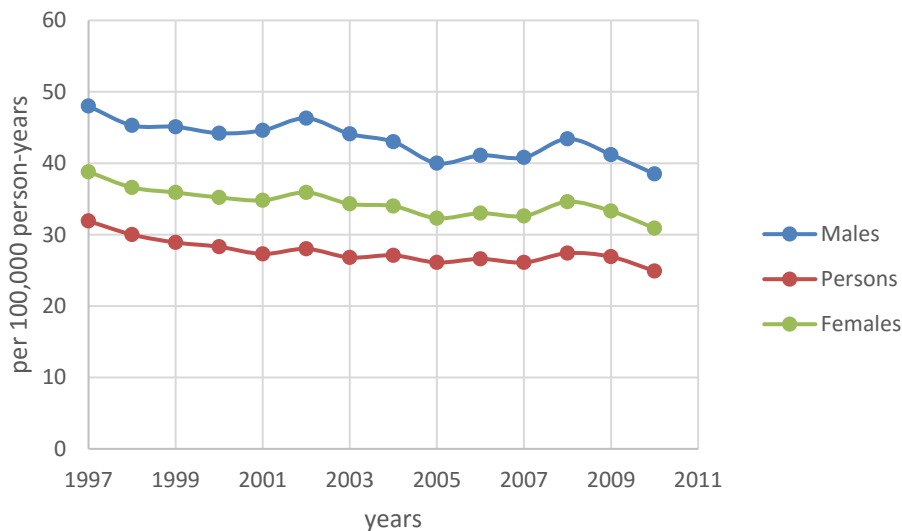


Figure 1 Death rates for diabetes as the underlying cause of death in Australia, 1997-2010²¹

1.1.5 Drug treatment for T2DM

The aim of the treatment in DM is to achieve normal or near normal blood glucose levels, to ameliorate the symptoms of hyperglycaemia, to reduce the risk of microvascular and macrovascular complications, and to reduce mortality and improve the quality of life. In T2DM, this may be achieved by lifestyle modification (i.e. diet and exercise), oral medications and insulin injections; in T1DM the ‘missing insulin’ has to be replaced, resulting in life-long insulin injections.

Early initiation of pharmacologic therapy is associated with improved glycaemic control and reduced long-term complications in T2DM. Drug classes used for the treatment of T2DM include in

Table 1, which is summarised based on the recommendations/statements of Australian Medicines Handbook (AMH, 2016), General practice management of type 2 diabetes 2014-15 (Diabetes Australia), Anti-diabetic agents for use in type 2 diabetes 2016 (Canadian Diabetes Association) and the primary literature.

Table 1 Drugs for T2DM

Class/drug	Expected decrease in HbA _{1c} (mmol/mol)	Effect on weight	Hypoglycaemia	Comments
Oral				
Metformin	10-20	Nil (or decrease)	Negligible risk as monotherapy.	<ul style="list-style-type: none"> Improved cardiovascular outcomes in overweight subjects; GI adverse effects are common; Lactic acidosis is very rare.
Sulfonylureas (glibenclamide, gliclazide, glimepiride, glipizide)	10-20	Increase	Glibenclamide and glimepiride may cause rates of hypoglycaemia.	<ul style="list-style-type: none"> All insulin secretagogues reduce glycaemia similarly.
Dipeptidyl peptidase-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin)	5-10	Nil	Negligible risk as monotherapy.	<ul style="list-style-type: none"> Improved post-prandial control; Caution with Saxagliptin in heart failure; Rare cases of pancreatitis; Long-term safety and efficacy data are limited.
Thiazolidinediones (pioglitazone, rosiglitazone)	5-15	Increase	Negligible risk as monotherapy.	<ul style="list-style-type: none"> Between 6 and 12 weeks required to achieve full glycaemic effect; Ineffective in up to 30% of patients; Adverse effects include cardiovascular controversy (rosiglitazone), increased LDL-C (rosiglitazone); Rare risk of bladder cancer with pioglitazone.
Acarbose	5-10	Nil	Negligible risk as monotherapy.	<ul style="list-style-type: none"> Reduces postprandial hyperglycaemia Associated with GI side effects; Not recommended as initial therapy in people with marked hyperglycaemia (HbA_{1c}>8.5%).
Sodium-glucose co-transporter 2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)	5-10	Decrease	Low risk with monotherapy (increased risk in combination with a sulfonylurea or insulin);	<ul style="list-style-type: none"> Rely on adequate renal function; Increase urinary glucose, adverse effects include vaginal candidiasis and urinary tract infection; Long-term safety and efficacy data are lacking.
Parenteral				

Insulin	15-40	Increase	Significant risk.	<ul style="list-style-type: none"> • Greater risk of hypoglycaemia and weight gain than sulfonylureas.
Glucagon-like peptide 1 analogues (exenatide, liraglutide)	5-15	Decrease	Negligible risk as monotherapy.	<ul style="list-style-type: none"> • Improved post-prandial control; • GI side effects are common; • Rare cases of pancreatitis; • Long-term safety and efficacy data are limited.

An increasing range of medications for the treatment of T2DM are now available, and each medication has its own efficacy in the treatment of T2DM (Table 1). Sulfonylureas, thiazolidinediones (TZDs), and insulin are more likely to be associated with weight gain when compared to the other anti-diabetic medications.²²⁻²⁴ Dipeptidyl peptidase-4 (DPP-4) inhibitors showed less potency in reduction of HbA1c than metformin or sulfonylureas.²⁵ Sulfonylureas are associated with a high risk of severe hypoglycaemia as monotherapy and in combination with metformin (compared to metformin plus a DPP-4 inhibitor or a sodium-glucose co-transporter 2 (SGLT-2) inhibitor).^{25, 26} SGLT-2 inhibitors increased the risk of genital mycotic infections compared to all other monotherapies and metformin-based combinations.²⁷ Both metformin and glucagon-like peptide-1 (GLP-1) receptor agonists are associated with a higher risk of gastrointestinal adverse effects.²⁵

Metformin is effective in correcting hyperglycaemia and has a long history of use, demonstrated safety and tolerability. Besides, metformin is associated with lower cardiovascular mortality compared to sulfonylureas.²⁸⁻³⁰ In addition, two ongoing randomized, double-blind clinical trials [Metformin in CABG trial, MetCAB (NCT01438723) and Glycometabolic Intervention as Adjunct to Primary Percutaneous Intervention in ST Elevation Myocardial Infarction Trial, GIPS-III (NCT01217307)]³¹ will help to elucidate whether metformin can reduce infarct size and improve left ventricular function after ischaemia-reperfusion injury.³² Metformin treatment produced more weight loss in patients with T2DM versus TZDs or sulfonylureas monotherapy.²⁷ Metformin also costs less in comparison to most of the other anti-diabetic medications (sulfonylureas and TZDs are also relatively low cost).³³

Metformin is the medication of choice and recommended to all patients with T2DM unless contraindicated and not tolerated.⁹ Second- and third-line agents may be necessary in addition to metformin when T2DM is poorly controlled. When additional agent(s) are required,

an individualised approach is recommended based on patient needs (i.e. efficacy, risk of hypoglycaemia, major side effects, weight gain and costs); the agent should work in a different way and be chosen to work synergistically.⁹

Achieving glycaemic control has been shown to both prevent and delay the progression of CKD.^{24, 34, 35} Intensive diabetes management with the goal of achieving near normoglycaemia has been shown to delay the onset of microalbuminuria and the progression of microalbuminuria to macroalbuminuria in patients with T2DM in a large prospective randomised study.⁹ Besides, it is important to note that CKD can influence the pharmacokinetics of most of the anti-diabetic medication (except gliclazide, glipizide, pioglitazone, rosiglitazone and linagliptin), which potentially presents as enhanced risk of hypoglycaemia, drug-to-drug interactions and/or side effects.³⁶ Therefore, the daily dosage of each anti-diabetic medication should be reduced according to the renal impairment. In Australia, the dosage recommendation is based on patients' creatinine clearance (CrCl) (Table 2). The Australian Medicines Handbook (AMH) classifies reduction in the kidney function based on the estimation of CrCl into three categories; mild (25-50 ml/min), moderate (10-25 ml/min) and severe (< 10 ml/min). CrCl is used to guide the medication dosage adjustment in patients with renal impairment.

Table 2 Anti-diabetic medications dosing recommendations in renal impairment

AMH 2016				Product information	
Medications	Maximum daily dosage with normal renal function	Renal impairment, dosage recommendation (if any)	Contraindicated in renal function of	Renal impairment, dosage recommendation (if any)	Contraindicated in renal function of
Metformin	3000mg	CrCl 60-90 ml/min, 2000 mg/day; CrCl 30-60 ml/min, 1000 mg/day; CrCl 15-30 ml/min, 500 mg/day.	CrCl < 15 ml/min	N/A	CrCl < 60 ml/min
Glibenclamide	20 mg *	Gliclazide or glipizide preferred.		N/A	Severe renal impairment
Gliclazide	320mg			***	
Glimepiride	4mg *			N/A	CrCl < 30ml/min
Glipizide	40mg			***	
Pioglitazone	45mg			***	
Rosiglitazone	8mg	***		****	
Alogliptin	25mg	CrCl 30-50 ml/min, 12.5mg/day; CrCl < 30 ml/min, 6.25 mg/day.		CrCl 30-50 ml/min, 12.5mg/day; CrCl < 30 ml/min, 6.25 mg/day.	
Linagliptin	5mg	***		***	
Saxagliptin	5mg	CrCl < 50 ml/min, 2.5mg/day.		N/A	CrCl < 60 ml/min
Sitagliptin	100mg	CrCl 30-50 ml/min, 50 mg/day; CrCl < 30 ml/min, 25 mg/day.		CrCl 30-50 ml/min, 50 mg/day; CrCl < 30 ml/min, 25 mg/day.	
Vildagliptin	100mg	CrCl < 60 ml/min, 50 mg/day.		eGFR < 60 ml/min, 50mg/day.	
Exenatide	20µg	CrCl 30-50 ml/min, possible increased risk of adverse effects.	CrCl < 30 ml/min	CrCl > 30 ml/min***	CrCl < 30 ml/min
Liraglutide	1.8mg	****		CrCl < 30 ml/min****	

Canagliflozin	300mg	CrCl 45-60 ml/min, 100 mg/day.	CrCl < 45 ml/min	CrCl >60 ml/min or eGFR >60 ml/min/1.73m ² : ***; CrCl 45-60 ml/min or eGFR 45-60 ml/min/1.73m ² : 100mg/day.	CrCl < 45 ml/min or eGFR <45 ml/min/1.73m ²
Dapagliflozin	10mg	N/A	CrCl < 60 ml/min	CrCl >60 ml/min or eGFR >60 ml/min/1.73m ² ***	CrCl <60 ml/min or eGFR <60 ml/min/1.73m ²
Empagliflozin	25mg	N/A	CrCl < 45 ml/min	eGFR >45 ml/min/1.73m ² ***	eGFR <45 ml/min/1.73m ²
Acarbose	150mg	N/A	CrCl < 25 ml/min	N/A	CrCl < 25 ml/min
Insulins		**		**	

The dosage recommendation is not including for (i) initiation of the drug; (ii) children; (iii) controlled release product; (iv) in combination with other anti-diabetic medications. Some of the drug should be given in divided dosage instead of one dose with the maximum dosage.

* Avoid glibenclamide/glimepiride in renal impairment due to the increased risk of hypoglycaemia;

** May require dosage reduction;

*** No dosage adjustment required;

**** Limited data in patients with renal impairment.

1.2 **Metformin**

Metformin, which belongs to the class of biguanides, has been used widely in the treatment of T2DM. It has been found to be safe and efficacious both as monotherapy and in combination with other oral anti-diabetic medications and insulin. It offers the therapeutic effect of glycaemic control without inducing hypoglycaemia or weight gain.³⁷ Besides, the drug has shown advantages of counteracting the cardiovascular complications associated with diabetes and producing a reduction in the risk of diabetes-related morbidity and mortality.³⁷⁻³⁹ It is recommended as the first choice for patients with diagnosed of T2DM in Australia,⁹ European countries, United Kingdom (UK) and United States (US).⁴⁰ But lactic acidosis (LA), as a rare adverse effect associated with metformin, is the major barrier for practitioners to prescribe this drug.

1.2.1 **Mechanism of action**

Metformin does not stimulate insulin release but does require the presence of insulin to exert its antihyperglycaemic effect.⁴¹ It mainly reduces hepatic glucose production and increases peripheral utilisation of glucose.⁴² The exact mechanism of action of metformin remains obscure. There are several possible biological activities have been suggested in both human and animal studies, which include reducing gluconeogenesis, increasing glucose uptake and utilisation in skeletal muscle, and delaying of intestinal glucose absorption.

1.2.1.1 **Metformin's effect on liver**

Metformin's overall antihyperglycaemic effect is to reduce the rate of hepatic gluconeogenesis in patients with T2DM, thereby, decreasing endogenous glucose production, and lowering both fasting and postprandial plasma glucose.⁴³⁻⁴⁷ In clinical studies, metformin treatment lowered

the glucose production by 25% to 30%.^{43, 47} Another study showed that metformin therapy decreased endogenous glucose production by a mean of 19%, while the fasting and postprandial plasma glucose concentrations decreased by 20% and 25%, respectively.⁴² Animal studies showed similar results in reducing gluconeogenesis as those found in clinical studies. Several mechanisms have been proposed to explain the inhibitory action on hepatic gluconeogenesis, including changes in enzyme activities⁴⁸⁻⁵⁰ or a reduction in hepatic uptake of gluconeogenic substrates.⁵¹

Several possible mechanisms in inhibiting hepatic gluconeogenesis by metformin in the intracellular environment have been proposed. Metformin inhibits the respiratory chain complex I in the mitochondria (Figure 2), which results in reducing adenosine triphosphate (ATP) levels and increasing adenosine monophosphate (AMP). Gluconeogenesis is reduced as decreased ATP levels limit glucose synthesis; besides, decreased ATP and increased AMP levels lead to reduced activity of pyruvate carboxylase and fructose-1, 6-biphosphatase, which are required in gluconeogenesis.^{52, 53} It was reported recently that metformin inhibited the redox shuttle enzyme, mitochondrial glycerophosphate dehydrogenase (mGPD), resulting in an increased cytosolic redox state. This impairs the conversion of lactate to pyruvate, leading to decreased gluconeogenesis and accumulation of lactate,^{54 52, 55} which is associated with increased risk of LA. The inhibition of mGPD also contribute to the effect of decreased ATP and increased AMP levels.

Besides, metformin also decreased gluconeogenesis via an adenosine monophosphate-activated protein kinase (AMPK) dependent pathway (Figure 2). It has been proposed that the liver kinase B1/adenosine monophosphate-activated protein kinase (LKB1/AMPK) pathway mediates the action of metformin in hepatic gluconeogenesis.^{56, 57} The decreasing ATP and increasing AMP level activates the AMPK which suppresses the lipogenesis gene expression in the nucleus and acetyl-CoA carboxylase (ACC, lipogenic enzymes) activity, thus leading to

decreased lipogenesis.⁵⁸ A more recent study showed that intra-duodenal infusion of metformin activated the duodenal AMPK glucagon-like peptide-1 receptor protein-kinase-A dependent signal pathway to lower hepatic glucose production and plasma glucose in rat models of obesity and diabetes.⁵⁹

Besides, studies have suggested that metformin stimulates glycogenolysis and glycolysis in short-term periods, and ameliorates hyperglycaemia and insulin resistance as long-term effects via AMPK activation.^{53, 57, 60, 61} It has been suggested that metformin may act on the AMPK cascade and activate the catabolic pathways, such as glycogenolysis and glycolysis.⁶² Also, a study suggested that the reduction of glycogenolysis in T2DM was associated with decreased cycling of glucose 6-phosphatase (G6Pase), which was required for the production of a phosphate group and glucose; therefore, it reduced the glucose production. It was reported that metformin could increase levels of the active forms of both glycogen synthase and phosphorylase, indicating increased glycogen turnover.⁶³

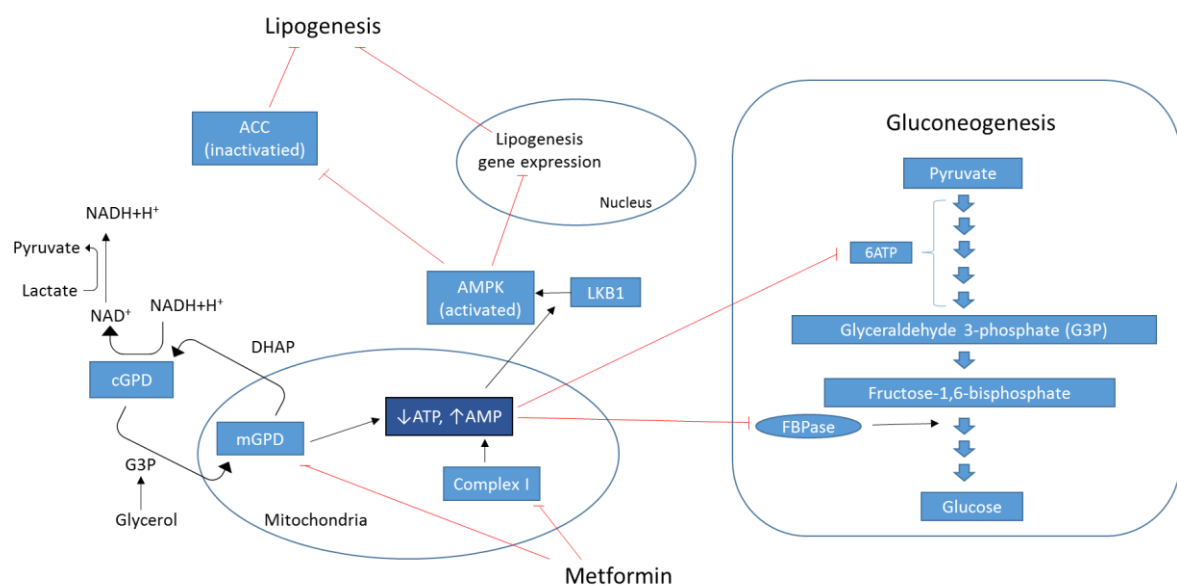


Figure 2 Potential molecular mechanisms of the action of metformin in gluconeogenesis and lipogenesis

Metformin inhibits the respiratory chain complex I in the mitochondria, which results in reducing ATP levels and increasing AMP. This lead to reduced activity of pyruvate carboxylase and fructose-1, 6-

biphosphatase.^{52, 58} The decreasing ATP and increasing AMP level also activates AMPK, which suppresses the lipogenesis gene expression in the nucleus and ACC activity, thus leading to decreased lipogenesis.⁵⁸ Metformin also inhibits mGDP, resulting in an increased cytosolic redox state, which impairs the conversion of lactate to pyruvate⁵⁴ and contributes to the result of decreased ATP and increased AMP levels. ACC: acetyl-CoA carboxylase; ATP: adenosine triphosphate; AMP: adenosine monophosphate; mGPD: mitochondrial glycerophosphate dehydrogenase

1.2.1.2 Metformin's effects on other tissues

Metformin has been reported to act on other tissues, including skeletal muscle and adipose tissue. Several studies have showed that administration of metformin enhances glucose uptake and glycogen synthesis in the muscle of diabetic animals^{64, 65} and patients with T2DM.⁶⁶ It has been suggested that most of insulin-stimulated glucose utilisation happens in skeletal muscle,^{67, 68} which may be attributed to the AMPK pathway. Furthermore, studies found that metformin affected lipid metabolism and turnover in skeletal muscles, which may be related to the suppression effect of metformin on the fatty acid oxidation in oxidative muscles.⁶⁹

Although adipose tissue is not a major site of metformin's action, metformin appears to have effects on it. Metformin has been shown to increase lipolysis, which may contribute to insulin sensitisation through the decrease of systemic free fatty acid levels; and it has been shown inhibition effect on lipogenesis in subcutaneous fat depot, which may contribute to reduced fat mass.^{69, 70} Metformin may also impact on the endocrine function of adipose tissue through the modulation of adipokine synthesis or excretion, including leptin, adiponectin and visfatin.⁶⁹ The activation of AMPK by metformin could also affect adipose tissue.

Besides, adipose tissue dysfunction contributes to the pathophysiology of polycystic ovary syndrome (PCOS). The cause of PCOS is not completely understood; while PCOS is associated with elevated levels of insulin in the blood. When the blood glucose level does not respond to normal level of insulin, the pancreas produces more insulin, which will cause excess production of insulin (called hyperinsulinemia). Insulin resistance and hyperinsulinemia can

occur in women with PCOS. Metformin is also used to treat PCOS in selected situations. It appeared to affect ovarian function through the alleviation of insulin excess acting upon the ovary and through direct ovarian effects.^{71, 72} Long-term metformin treatment may increase ovulation, improve menstrual cycles and reduce serum androgen levels in these patients.⁷³

1.2.2 Pharmacokinetics

The pharmacokinetic properties of metformin have been investigated in healthy subjects and also in patients with T2DM. The mean half-life ($t_{1/2}$) of metformin in plasma has been reported as approximately 5 hours.⁷⁴

Metformin is found to be poorly absorbed from the stomach, but the small intestine is suggested as the site for most absorption of the drug.⁷⁵ It has been reported that metformin concentration is high in the small intestine^{76, 77} and decreases the intestinal absorption of glucose,⁷⁸ which leads to lower postprandial blood glucose levels. Studies found that hepatic uptake and renal excretion of metformin are mediated by organic cation transporters (OCTs),⁷⁹ which are found in the small intestine,⁷⁹⁻⁸¹ the liver,^{79, 82} the skeletal muscle⁷⁹ and the kidney.^{79, 83} At therapeutic doses of oral metformin, steady-state plasma concentrations of metformin reaches in 24 to 48 hours and are generally less than 1 $\mu\text{g/mL}$ (average steady state concentration); even in maximum therapeutic doses (3,000 mg per day), metformin plasma levels would not generally exceed 5 $\mu\text{g/mL}$.⁸⁴ The blood glucose lowering effect of metformin develops over at least 10 days,^{85, 86} suggesting that metformin has a long residence time in the liver or other compartments.⁷⁴

Metformin does not bind to plasma proteins, which is due to its low lipophilic molecular structure. The actual volume of distribution (V_d) of oral metformin following multi-dosing has been reported as approximately 300 L, which indicated that there was considerable tissue

uptake of metformin.⁷⁴ Metformin is slowly taken up into erythrocytes in previous studies.^{87, 88} The peak concentrations in plasma would be much higher than in erythrocytes after a single dose; with long-term dosing, the concentrations of metformin in erythrocytes would have much less fluctuation in erythrocytes than in plasma.⁸⁷ Besides, the plasma concentration of metformin was undetectable 24 hours after a single dose oral administration; while it remained detectable in erythrocyte up to 48 hours.⁸⁷ The relatively stable concentrations in erythrocytes should be able to be detected in patients after exposure to metformin over 1 to 3 days.⁷⁴ There was a doubt that the clearance of metformin would have been slowed down due to its distribution into erythrocyte. But the clearance of metformin is four to five times more quickly comparing to creatinine, it would not be necessary to worry about the accumulation of metformin in erythrocyte.⁸⁹

Metformin does not undergo metabolism in either healthy humans or diabetic patients.⁸⁴ Metformin undergoes rapid renal excretion, which is the major mode of elimination of metformin. The kidney function is critical for the elimination of metformin. As a small and low lipid soluble molecule, metformin is filtered at the glomerulus and undergoes passive resorption; and the uptake of metformin is mediated by cation transporters in the kidney.⁷⁴ A dosage reduction of metformin is required in patients with kidney disease.

1.2.3 Metformin in clinical use

Metformin is mainly used in the treatment of T2DM. It is the most commonly prescribed oral anti-diabetic medications, and was also one of the top 10 commonly prescribed medicines in Australia in 2014.⁹⁰ Metformin is also used for other indications, such as PCOS.

1.2.3.1 Clinical benefits of metformin

Besides its anti-hyperglycaemic effect, clinical studies have shown the benefits of metformin in patients with complications including micro- and macrovascular complications,⁹¹ and the potential clinical advantages in those with cardiac disease and heart failure.³⁹

The United Kingdom Prospective Diabetes Study (UKPDS) (a landmark study of the effect of different diabetes therapies on vascular complications in people with T2DM) showed that metformin (with intensive glucose control) appeared to decrease the risk of diabetes-related endpoints in overweight patients, and was associated with less weight gain and fewer hypoglycaemic attacks compared to insulin and sulphonylureas.^{37, 92} In addition, metformin monotherapy showed significant decreases in any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction), all-cause mortality, and stroke, in comparison to chlorpropamide, glibenclamide, or insulin.³⁷ In their 10 years post-trial follow-up report, metformin still showed its advantages compared to other diabetic medications.⁹² Studies elsewhere have also reported significant improvement of all-cause mortality and cardiovascular mortality in metformin-treated patients.^{93, 94}

Studies have shown that metformin reduces the risk of hospitalisation for cardiovascular disease,⁹⁴ stroke,⁹⁵ and myocardial infarction.⁹⁶ An observational study in elderly patients with DM and heart failure found that metformin reduced hospital readmission and lowered the death rate during the years after initial hospitalisation.⁹⁷

Metformin has shown effect on anti-oxidative stress. These effects of metformin may also contribute to the treatment of clinical conditions such as inflammation, neurodegeneration (Alzheimer's disease and Parkinson's disease) and tumour formation.⁹⁸ Metformin may also

improve the lipid profile,^{44, 99} by reducing circulating triglycerides and free fatty acids, although so far there is no consensus on evidence to confirm these effects.

1.2.3.2 Side effects of metformin

Gastrointestinal side effects are the most common adverse effects with metformin treatment; these include nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.^{84, 100} These undesirable effects occur most frequently during the initiation of therapy and generally resolve spontaneously after continuous treatment. Malabsorption of vitamin B₁₂ is another common side effect has been observed, which was reported to reduce in intestinal absorption of vitamin B₁₂ in up to 30% of patients, in patients with long-term metformin therapy.^{101, 102}

1.2.4 Lactic acidosis and its relation with metformin

Although metformin is recommended as the first choice in treating T2DM, a common conundrum for practitioners in prescribing metformin is that it may cause LA. The concern of prescribing metformin may be affected by phenformin, which was another biguanide used to treat T2DM. Phenformin, however, was withdrawn from the market due to its high incidence of LA and deaths. Metformin was removed from the market in US in 1977 and many other countries; Australia recommended severe restrictions on its use. In 1995, metformin was reintroduced to the market in the US.¹⁰³

Metformin-associated LA (MALA) and metformin-induced LA (MILA) were used to describe the LA in metformin users. ‘Metformin-associated’ would mostly refer to situations of both elevated metformin concentration and associated pathology of LA; while ‘metformin-induced’ was used in describing LA cases with high plasma metformin concentrations and no

other potentially causative aetiologies.¹⁰⁴ It has been reported that LA occurs in patients (without other complications) with metformin overdose.^{105, 106}

At therapeutic dosage, the incidence of LA among patients prescribed metformin is thought to be 2-9 cases per 100,000 patient-years, this range was referred to generally as ‘the incidence of MALA’. But the reported incidence of LA in metformin users largely varied in studies, ranging from 1.5 to 530 per 100,000 patient-years.^{26, 107-111} A study conducted in a tertiary hospital in Queensland (Australia) reported an estimated incidence of 530 per 100,000 patient-years.¹⁰⁷ The selection of patients who were admitted to the hospital mostly resulted a higher calculated rate of incidence. A recent pharmacoepidmiological study in Japan reported that the crude incidence of LA was 5.95 per 100,000 patient-years, which based on 30 cases of LA among 280,000 treated T2DM patients with more than 500,000 patient-years of follow-up.¹¹² The authors also pointed out metformin was not associated with risk of LA; however, patients with T2DM and CKD were seven-fold more likely to develop LA than those without CKD.

A review summarised the mortality of rate of LA in metformin users, which varied markedly from literatures (from 3% to 61%), but the rate was more frequently reported at 33%.¹¹³ The challenge to correctly determine the factors with which mortality is associated (rather than determining the mortality rate itself). The contribution of metformin in these LA cases may be overemphasised: (i) in most of the cases, patients were reported with other clinical conditions which could lead to LA; and (ii) the metformin concentration was not usually measured. The term “mixed LA in metformin-treated patients” has been used, suggesting that “mixed” would better reflect the combination of other factors.¹¹³ In addition, there is no randomised controlled trial has been conducted to assess the association between metformin and LA, and so far, no correlation between metformin and lactate level has been established.

1.2.4.1 Lactate and lactic acidosis

The normal level of lactate is about 0.3 - 1.3 mmol/L with a balance between production and clearance. The liver removes approximately 70% of lactate.¹¹⁴ In the liver, under normal conditions, more than half of lactate in the body is converted to glucose (gluconeogenesis) and half is further metabolised to CO₂ and water in the citric acid cycle. Other tissues can use lactate as a substrate and oxidise it to CO₂ and water, and mitochondria-rich tissues (such as skeletal and cardiac myocytes, proximal tubule cells) remove lactate by converting it to pyruvate. The kidney is also responsible for the removal of lactate, which undergoes renal uptake and metabolism and urinary excretion.¹¹⁵ It has been suggested that acidosis depressed hepatic uptake of lactate, but increased renal lactate metabolism.¹¹⁵ Any dysfunction of the liver and kidney may affect the clearance of lactate.

Besides, the skeletal muscle seems to play a role in both production and clearance of lactate.¹¹⁶ The brain and adipose tissues have shown to contribute in the lactate turnover.¹¹⁶

LA, a form of metabolic acidosis, develops with the accumulation of lactic acid in blood as a cause of acid-base disorder. Clinically, if the blood lactate level reaches to 2-5 mmol/L, it is considered as hyperlactatemia; while it is LA when the level is greater than 5 mmol/L with pH < 7.35.^{117, 118} Hyperlactatemia can occur in the setting of intact buffering systems, adequate tissue perfusion or oxygenation.^{117, 119} LA can occur under conditions of excessive tissue lactate production or impaired hepatic metabolism of lactate.^{117, 119}

Traditionally, LA is classified into Type A and Type B LA (Cohen & Woods, 1976)¹²⁰ with the main differentiation on whether the tissue oxygen delivery is sufficient or not (Table 3).^{118, 121, 122}

Type A LA refers to circumstances in which there is clinical evidence that tissue oxygen delivery is inadequate (anaerobic acidosis). Hypoxaemia, anaemia and shock can lead to type A LA.^{118, 121} When the oxygen supply is insufficient, after glucose being metabolised into pyruvate in cytoplasm, the further metabolism of pyruvate inside mitochondria will be slowed down, and pyruvate will be converted to lactate (with conversion of nicotinamide adenine dinucleotide from reduced form to oxidised form, NADH to NAD⁺).^{122, 123} The conversion of NADH to NAD⁺ is important as it regenerates NAD⁺ needed for glycolysis to continue. This process is known as anaerobic metabolism and results in a small net ATP production.¹¹⁴ The mitochondrial reactions are unable to have normal function due to inadequate oxygen.

Type B LA refers to the situations where there is no clinical evidence of insufficient tissue oxygen delivery (aerobic acidosis), which is usually caused by (i) underlying disease, such as renal failure, liver failure and short-gut syndrome; (ii) drugs or toxicants; or (iii) metabolic derangements involving failure to clear lactate.^{118, 121}

Table 3 Classification of lactic acidosis^{120, 122}

Classifications	Causes
Type A: Clinical evidence of impaired tissue oxygenation	
	<ul style="list-style-type: none"> Anaerobic muscle activity (increased oxygen demands) Tissue hypoperfusion (decreased oxygen delivery) Tissue hypoxia (decreased available oxygen or carrying capacity)
Type B: No clinical evidence of impaired tissue oxygenation	
B1	<ul style="list-style-type: none"> Underlying disease Renal failure; liver failure; malignancy; HIV; short-gut syndrome
B2	<ul style="list-style-type: none"> Drugs and toxins Alcohols; beta-agonists; biguanides; carbon monoxide; catecholamines; cocaine; cyanide/nitroprusside; isoniazid; linezolid; nalidixic acid; nucleoside reverse transcriptase inhibitors; propofol; salicylates; theophylline; valproate
B3	<ul style="list-style-type: none"> Inborn errors of metabolism Defects in gluconeogenesis, pyruvate dehydrogenase, tricarboxylic acid cycle, respiratory chain

1.2.4.2 Metformin's effect on lactate level: possible mechanism

The potential intracellular mechanism of metformin affecting lactate production was proposed in the studies which were conducted to discover the mechanism of its glucose lowering effect. Early studies suggested that the mechanism of metformin in increasing plasma lactate level related to the inhibition of mitochondrial respiration in tissues responsible for lactate removal.^{53, 124, 125} A recent study reported that both acute and chronic metformin treatment inhibit mGPD, limiting lactate and glycerol contributions to hepatic gluconeogenesis, which resulted in increased lactate levels.⁵⁵ The inhibition of mGPD halted the glycerophosphate shuttle and lead to accumulation of cytosolic NADH, which was unfavourable for the conversion of lactate to pyruvate by lactate dehydrogenase. The suggested mechanism could explain the potential risk of LA associated with metformin use.

1.2.4.3 Treatment for lactic acidosis in metformin-treated patients

It has been suggested that the mainstay of LA therapy in metformin users was normalising the acid-base imbalance and treating the triggering factors for LA.¹²⁶ Various treatments have been used to treat LA in metformin-treated patients; however, there is no consensus in managing in this acute condition.

Administration of bicarbonate and mechanical ventilation have been used to correct acidosis.¹²⁷ But bicarbonate is not routinely recommended, since it may promote lactate accumulation and further intracellular acidification.^{128, 129} Extracorporeal treatment, such as haemodialysis and haemofiltration, is quite common to be used in treating LA. A recent systematic review¹²⁹ reported that intermittent haemodialysis was the predominant extracorporeal treatment, followed by continuous renal replacement therapy. The ideal characteristics of chemicals removable in extracorporeal elimination (i.e. haemodialysis and

haemofiltration) are a low volume of distribution, a low percentage of protein-binding and a small molecule (which could get through the dialysis membrane).¹³⁰ Although metformin has a small molecular size and is associated with low protein-binding, it has a relatively large volume of distribution, which becomes a limiting factor in extracorporeal elimination.^{126, 129} However, compared to bicarbonate administration, extracorporeal treatment could correct the acidosis more rapidly and be predictable.¹²⁹ The extracorporeal treatment would also correct the electrolyte abnormalities,¹³¹ and be beneficial in supporting impaired renal function.¹³⁰

1.2.5 Recommendations in product information of metformin and guidelines

Current official product information recommends that metformin should be avoided or used with caution/dosage adjustment in patients with coexisting conditions, as shown in Table 4, that are likely to increase the risk of LA.

Table 4 Contraindications and precautions of metformin ^{84, 132}

	Conditions listed in the official product information	Australian Medicines Handbook (2012)	Australian Medicines Handbook (online 2016)	American Hospital Formulary Service (AHFS) Drug Information (online 2016)
Contraindications	Acute conditions with potential to alter renal function, such as:			
	• dehydration;	√	√	√
	• severe infection;	√ and trauma	N/A	√
	• shock;	√	√	√
	• intravascular administration of iodinated contrast materials	√	N/A	√
	Acute or chronic disease which may cause tissue hypoxia, such as:			
	• cardiac failure;	Moderate to severe heart failure	Severe Heart failure	Acute heart failure, congestive heart failure
	• recent myocardial infarction;	√	√	√
	• respiratory failure;	√	N/A	Respiratory distress
	• gangrene;	N/A	N/A	N/A
	• shock;	√	√	√
	• acute significant blood loss;	N/A	N/A	N/A
	• pulmonary embolism;	√	√	N/A
	• pancreatitis;	N/A	N/A	N/A
	• sepsis	√	√	√
	Severe hepatic insufficiency (acute alcohol intake; alcoholism)	√	√	√
	Diabetic coma and ketoacidosis	√	√	√
	Hypersensitivity to the drug	N/A	N/A	√
	History or states associated with lactic acidosis, such as shock or pulmonary insufficiency	√	√	√
	Renal failure or renal dysfunction (creatinine clearance < 60mL/min)	Contraindicated in CrCl < 30 mL/min.	Contraindicated in CrCl < 15 mL/min.	Contraindicated in eGFR < 30 mL/min per 1.73m ² .
	Lactation	Save in breastfeeding	Save in breastfeeding	N/A
Precautions	Use in the elderly	√	√	√
	Discontinued 48 hours before elective major surgery and administration of iodinated contrast materials	√	Stop metformin before surgery	√

	Radiological studies using contrast media	√	N/A	√
	Surgical procedures	√	√	√

N/A: information is not available.

The listed conditions as contraindications and precautions are stated in the official product information of metformin (Glucophage®).

A number of contraindications to the use of metformin are listed in the product information. A few international studies have recently questioned the contraindications to the use of metformin, as it was not associated with a significant change in lactate levels in patients receiving metformin compared to other antidiabetic agents.¹³³⁻¹³⁵ It has been suggested that strict adherence to these recommendations may deny a valuable drug to many patients,¹³⁶ and conditions including myocardial infarction and stable coronary heart failure should not to be considered as absolute contraindications to use metformin.¹³³

The AMH, used as an evidence-based independent medicines reference in the Australian healthcare sector, has changed its recommendation to the prescribing of metformin since 2014. The previous warning regarding the usage of metformin in AMH was similar to that in the product information (Table 4), which recommended that the drug should be contraindicated in conditions including respiratory failure, severe infection or trauma, alcohol misuse, and moderate to severe heart failure. Overall, the caution of prescribing metformin suggested in the current AMH is lower compared to the recommendations in the previous versions (before 2014). Currently, it is suggested to use metformin with precautions in conditions which may alter renal function (eg dehydration, shock, sepsis) or increase risk of tissue hypoxia and acidosis (eg MI, severe heart failure, liver failure, pulmonary embolism, ketoacidosis), which may increase the risk of LA. Patients with severe hepatic impairment should avoid the use of metformin. Also, elderly patients should use it cautiously; and metformin should be stopped before surgery.

Dosage reduction of metformin is required in patients with CKD (AMH online 2016): a dosage no more than 2,000 mg per day for patients with a CrCl from 60 to 90 mL/min, or 1,000 mg per day for patients with a CrCl from 30 to 60 mL/min, or 500 mg per day for patients

with a CrCl from 15 to 30 mL/min; and metformin is not recommended to be used when the CrCl is lower than 15 mL/min.

The current diabetic management guideline (2014-15)⁹ from Diabetes Australia states that LA is uncommon, which may occur with dehydration and co-existing renal, liver or cardiovascular disease. Besides, this guideline recommended that renal impairment (eGFR < 30 mL/min per 1.73m²) is the only absolute contraindication to metformin.

Guidelines from other countries also show the concerns of LA to initiate/continue metformin, which are similar to the recommendations from AMH and Diabetes Australia. LA is the adverse effect which could lead to death, although the incidence is rare. The recommendations of “contraindications” of metformin in clinical guidelines from different countries varied slightly, mainly due to the quality of the evidence. Majority of the available evidence regarding LA in metformin-treated patients are from retrospective designed cross-sectional studies or case series, the strength of these evidence is being questioned, including the design of studies and the number of patients. To date, there is no randomised control trial including large number of population with long-term follow-up to investigate the relation between metformin and LA; while the contraindications stated in the PI or guidelines could be the ethical issue which may it unlikely to conduct a randomised control trial.

1.3 **Rationale**

A Cochrane review that included 347 comparative trials and cohort studies revealed no case of LA in 70,490 patient-years of metformin use or in 55,451 patients-years in the non-metformin group.¹³⁷ In that review, 57% of the studies excluded patients with renal impairment (defined as a creatinine level of greater than 132.6 µmol/L), 46% of cardiovascular disease, 13% of pulmonary disease, and 12% of age greater than 65 years. In fact, it is not unusual for patients

with diagnosis of T2DM to have other complications (as discussed above); and some of the conditions such as renal impairment and heart failure would also be associated with increased risk of LA. The contribution of metformin in altering lactate levels in patients with T2DM was not clear, especially in those with other underlying clinical conditions.

In spite of the well-established evidence regarding the benefits of metformin among patients with T2DM, the caution of LA may have become a barrier for practitioners to prescribe this drug. However, limited studies conducted in Australia have reported on the current usage of metformin in practice. It is important to clarify the clinical usefulness of metformin and its relation to LA in order to improve the safe use of this drug in all patients with T2DM.

Thus, this thesis was designed to explore the current usage of metformin in patients diagnosed with T2DM in Australia and investigate the cases of LA in metformin-treated patients. The specific objectives of the research were:

- To evaluate the prescribing patterns of metformin in patients with T2DM and to identify the potentially inappropriate prescribing of metformin;
- To identify potential cases of LA related to metformin use;
- To review and summarise the reported LA cases associated with metformin, and explore the potential association between LA and the use of metformin;
- To compare the lactate levels between patients with T2DM who were treated with metformin chronically and those who were not treated with metformin.

Part B

Chapter 2 Metformin usage in type 2 diabetes mellitus: are safety guidelines adhered to?

2 Abstract

Aim: To (i) evaluate the prescribing patterns of metformin in patients with type 2 diabetes mellitus (T2DM) and determine the prevalence of contraindications to its use, especially renal impairment, and (ii) identify potential cases of lactic acidosis (LA) related to metformin usage.

Method: This retrospective study reviewed all patients with a diagnosis of T2DM and taking metformin who were admitted to a major teaching hospital over an 8-month period. Data including demographics, medical conditions, medications at admission and discharge, and relevant pathology results, were extracted from medical records.

Results: A total of 301 patients (209 medical patients, 92 surgical patients) taking metformin were included. According to guidelines, approximately 31% and 21% of patients received metformin inappropriately (in the presence of contraindications or in excessive dosage) at admission and discharge, respectively. At admission, 65 patients (n=301, 21.6%) on metformin had at least one contraindication to its use, and 42 patients (n=254, 16.5%) were prescribed an excessive dosage according to their renal function. At discharge, 43 patients (n=301, 14.3%) continued on metformin with at least one contraindication and 21 patients (n=191, 11%) received an excessive dosage according to their renal function. Four patients had evidence of LA (plasma lactate concentration > 5.0 mmol/L and pH < 7.35) without clinical diagnosis.

Conclusion: Metformin was often used in patients with contraindications to its use, or in higher than recommended dosages. Reconsideration of the official prescribing information for metformin may be warranted as the risk of harm appears to be very low.

2.1 Introduction

Metformin, a biguanide anti-diabetic agent, is an insulin sensitiser which is used as the first-line oral medication in the treatment of type 2 diabetes mellitus (T2DM). In Australia, the prescribing of metformin has gradually increased,¹³⁸ largely because of its benefits over other anti-diabetic agents. In 2012, diabetes experts in the United States (US) and Europe declared that metformin is the first choice for all patients with T2DM.⁴⁰ The Australian National Health and Medical Research Council is considering a similar recommendation.¹⁰³ In particular, metformin does not cause weight gain and is generally associated with a low risk of hypoglycaemia. It has been shown that metformin-treated patients experienced significant reductions in the risk of myocardial infarction and diabetes-related, as well as all-cause, mortality.³⁷ The United Kingdom Prospective Diabetes Study (UKPDS) 10-year follow-up demonstrated the significant benefit on cardiovascular disease endpoints and total mortality in metformin-treated patients.⁹²

Despite the evidence base for the benefits of metformin, concerns still remain about its side effects, particularly the perceived risks of lactic acidosis (LA),^{139, 140} especially in patients with renal impairment. LA associated with metformin is a rare condition with an estimated prevalence of 4.3 cases per 100,000 patient-years.¹³⁷ However, LA has a 50% fatality rate^{111, 141} and hence most current guidelines¹⁴²⁻¹⁴⁵ recommend that metformin be avoided or used with dosage adjustment/ caution in patients with coexisting conditions that are likely to increase the risk of LA. Specifically, it is recommended that metformin should be avoided in patients with a creatinine clearance (CrCl) less than 30 mL/min¹⁴⁶ or estimated glomerular filtration rate (eGFR) less than 30 mL/min per 1.73 m²,¹⁴² severe hepatic impairment, moderate to severe heart failure, severe infection, ketoacidosis, and respiratory failure.⁸⁴ In addition, it is recommended that metformin should be used with caution in older people and in patients undergoing major elective surgery, with close monitoring of renal function.⁸⁴ Furthermore, it

is also recommended to avoid metformin in patients who are at a high risk of postoperative complications, such as sepsis or acute renal failure.⁴¹

In practice, a major dilemma is that strict limitations in metformin usage are presented in the official product information (PI) and current guidelines; however, the incidence of LA associated with metformin seemingly remains low, including in those whom contraindications exist.^{134, 135} Recent evidence suggested that these contraindications might be overly conservative.¹³³ Hence, the main aim of this study was to evaluate the local prescribing of metformin in patients with T2DM, and identify potential LA cases related to metformin usage. The specific objective was to determine if the prescribing of metformin was in accordance with current guidelines, especially in patients in whom renal impairment or contraindications exist.

2.2 Methods

This retrospective audit included patients with T2DM (International Classification of Diseases 10th Edition, ICD-10: E11) who were admitted to the Royal Hobart Hospital (RHH), Tasmania, between 1st January and 31st August 2012. RHH is the principal referral hospital in Tasmania; it has 550 beds serving around 240,000 people in the region. The study was approved by the Tasmania Health and Medical Human Research Ethics Committee (Reference number: H0012876).

Medical and surgical patients were included in the study if they met all of following criteria (Figure 3): (1) aged over 18 years and had T2DM; (2) were being treated with metformin at admission; and (3) had at least an overnight stay in the hospital. Patients with a primary diagnosis of acute kidney injury (AKI) were excluded. In patients who had more than one overnight admission during the study period, only the first admission record was included. Patients' medical records both at admission and discharge were reviewed. Data extracted

included demographics, medical conditions, medications at admission and discharge, and relevant pathology results (e.g. blood glucose, HbA1c, plasma lactate level, pH, eGFR, serum creatinine (SCr), albumin, total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT)). The reasons for admission identified from the medical record at admission were coded according to the ICD10. The medical history and other documentation during hospitalisation were paper based and noted without using codes.

In this study, inappropriate use of metformin was defined as having a contraindication to the use of metformin, identified according to: Australian Medicines Handbook (AMH) 2013 – metformin;¹⁴⁶ Diabetes Australia - current guidelines for the management of T2DM;¹⁴² Therapeutic Guidelines (TG);¹⁴⁷ and the official PI for metformin (Glucophage®)¹⁴⁸ (Table 5). Contraindications included: acute significant blood loss, cardiac failure, dehydration, diabetic ketoacidosis, gangrene, hepatic dysfunction, pancreatitis, pulmonary embolism, myocardial infarction, renal failure, respiratory failure, shock, sepsis, and severe infection.

Table 5 Contraindications for metformin usage in the official product information, Australian Medicines Handbook and the guidelines of Diabetes Australia and Therapeutic Guidelines

	Conditions listed in the official product information (Glucophage®)	Australian Medicines Handbook (2013)	Diabetes Australia (2012-2013)	Therapeutic Guidelines (2013)
Contraindications	Acute conditions with potential to alter renal function, such as:			
	• dehydration;	√	N/A	N/A
	• severe infection;	√ and trauma	N/A	N/A
	• shock;	√	N/A	√
	• intravascular administration of iodinated contrast materials	√	√	√
	Acute or chronic disease which may cause tissue hypoxia, such as:			
	• cardiac failure;	Moderate to severe heart failure	(Caution)	√
	• recent myocardial infarction;	√	(Caution)	√
	• respiratory failure;	√	N/A	√
	• gangrene;	N/A	N/A	√
	• shock;	√	N/A	√
	• acute significant blood loss;	N/A	N/A	√
	• pulmonary embolism;	√	N/A	√
	• pancreatitis;	N/A	N/A	√
	• sepsis	√	N/A	√
	Severe hepatic insufficiency (acute alcohol intake; alcoholism)	√	(Caution)	N/A
	Diabetic coma and ketoacidosis	√	√	N/A
	Hypersensitivity to the drug	N/A	√	N/A
	History or states associated with lactic acidosis, such as shock or pulmonary insufficiency	√	√	N/A
	Renal failure or renal dysfunction (creatinine clearance < 60mL/min)	Contraindicated in CrCl < 30 mL/min	Contraindicated in GFR < 30 mL/min	Contraindicated in CrCl < 30 mL/min
	Lactation	Safe in breastfeeding	N/A	N/A
Precautions	Use in the elderly	√	√	√
	Discontinued 48 hours before elective major surgery and administration of iodinated contrast materials	√	√	√
	Radiological studies using contrast media	√	√	√
	Surgical procedures	√	√	√

For the purpose of identifying contraindications, in the absence of a documented diagnosis, hepatic dysfunction was defined as biochemical evidence of hypoalbuminaemia and abnormal serum levels (greater than the upper level of normal) of at least two of the following:¹⁴⁹ total bilirubin, ALT, ALP or GGT. Moderate to severe cardiac failure was identified by patients' pharmacological treatment, which included an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, beta-blocker, and spironolactone with/without digoxin.¹⁵⁰ Renal function was identified by calculating the CrCl using the Cockcroft-Gault equation (CG equation). In cases where CrCl could not be calculated, eGFR was used. Metformin was considered contraindicated in patients with a CrCl less than 30 mL/min or eGFR less than 30 mL/min per 1.73 m². The dosage of metformin was considered inappropriate in: a dosage higher than 2 gram per day for patients with a CrCl between 60 to 90 mL/min or an eGFR between 60 to 90 mL/min per 1.73 m², or 1 gram per day for patients with a CrCl between 30 to 60 mL/min or an eGFR between 30 to 60 mL/min per 1.73m².¹⁴⁶ LA was identified when the plasma lactate concentration was > 5.0 mmol/L and pH < 7.35.^{117, 118}

In patients who underwent planned (elective) surgery, it was also determined whether metformin had been discontinued at least 48 hours prior to the surgery and restarted no earlier than 48 hours following the surgery, only after the renal function had been re-evaluated and found to be normal.¹⁴⁸

The data were summarised and analysed using Microsoft Excel 2010 and Statistical Package for Social Sciences (SPSS) for Windows version 20 (SPSS Inc., Chicago, Illinois, US).

2.3 Results

A total of 1274 admissions were recorded during the study period with coding as T2DM, and the medical records were paper based. After assessment against the study criteria, 301 patients were included (Figure 3). The mean \pm standard deviation (SD) age of the study sample was 68 ± 12.1 years (range: 24-98 years) and 60% were male (Table 6). The majority of patients (n=188, 62.4%) were aged 65 years or over, while 16 % (n=48) were aged 80 years or over. Of the 301 patients, 92 patients were admitted for surgery, 47 of whom underwent elective surgery. The most common reasons for admission included diseases of the circulatory system (n=87, 28.9%) followed by diseases of the endocrine system (n=28, 9.3%).

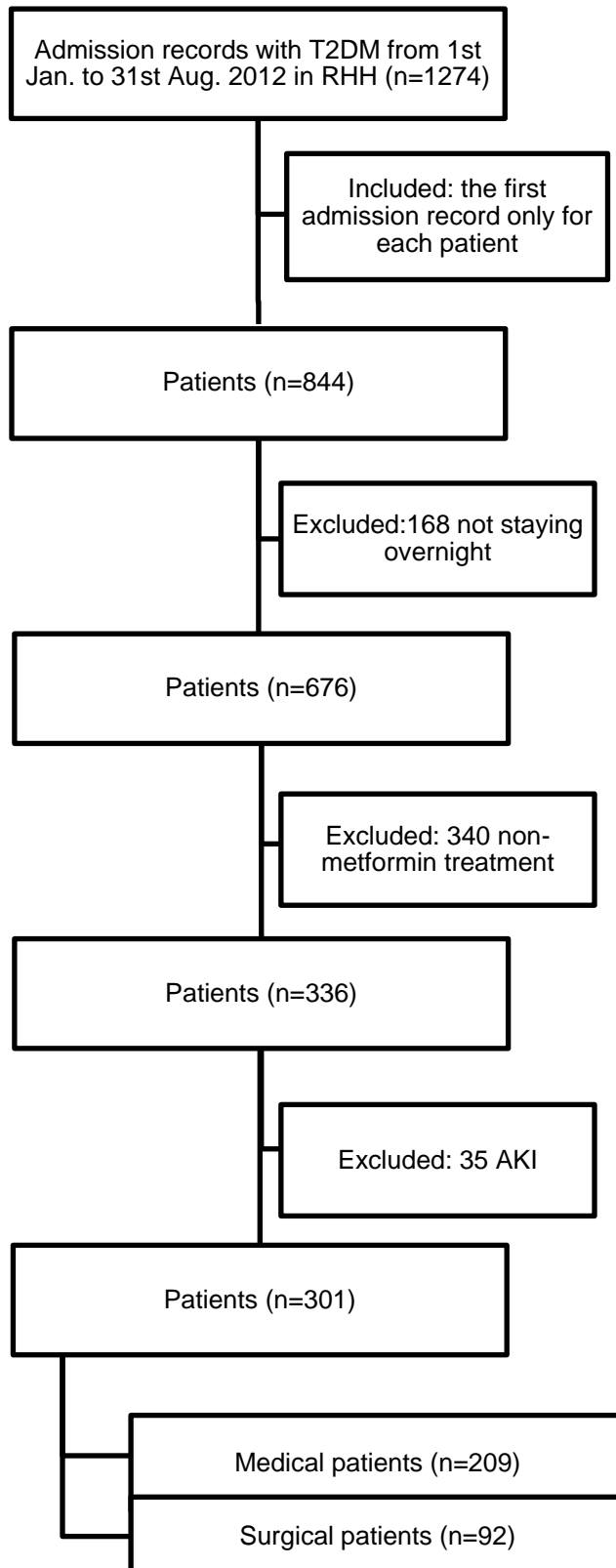


Figure 3 Patient selection

(AKI = acute kidney injury; DMR = digital medical record; RHH = Royal Hobart Hospital; T2DM = type 2 diabetes mellitus)

Table 6 Baseline characteristics of the study sample

Characteristics		Num. of patients (n) included [†]	Value
Age [Mean \pm SD; years]			68 \pm 12.1
Gender [male, %]			182, 60%
Weight [Mean \pm SD; kg]		172	89.8 \pm 26.0
Height [Mean \pm SD; cm]		63	167.4 \pm 10.7
BMI [Mean \pm SD; kg/m ²]		63	32.7 \pm 7.8
HbA1c [Mean \pm SD; %]		107	8.6 \pm 2.2
Lactate [Mean \pm SD; mmol/L]		114	2.1 \pm 1.5
Serum creatinine (SCr) [Mean \pm SD; mmol/L]		282	91 \pm 38
Number of regular medications			7 \pm 3
Number of PRN medications			1 \pm 1
Metformin dosage [Mean \pm SD; mg/day]		267	1506.8 \pm 662.1 [‡]
Duration of hospitalisation [Median, IQR; days]			5, 2-9
Reasons of admission (top 5) [number of patient (%)]	Disease of circulatory system (ICD10-I)		87 (28.9%)
	Endocrine, nutritional and metabolic diseases (ICD10-E)		28 (9.3%)
	Injury, poisoning and certain other consequences of external causes (ICD10-S & T)		25 (8.3%)
	Neoplasms (ICD10-C & D)		24 (8.0%)
	Diseases of respiratory system (ICD10-J)		20 (6.6%)
Other medications for T2DM treatment at admission [number of patient (%)]	Insulin		109 (36.2%)
	Sulfonylureas		96 (31.9%)
	Thiazolidinediones		15 (5.0%)
	DPP-4 inhibitors		12 (4.0%)
	Acarbose		0 (0)
	Exenatide		5 (1.7%)
Average num. of medications for T2DM treatment at admission			1 \pm 0.5
Average num. of medications for T2DM treatment at discharge			1 \pm 0.5

[†] n = 301, unless stated specifically; [‡] The dosage was not recorded in 35 patients.

IQR = interquartile range.

Of the 301 patients using metformin at admission, 114 patients (37.9%) were prescribed metformin as monotherapy for diabetes, 141 patients (46.8%) were on dual therapy, and 43 and 3 patients (14.3% and 1%) were on triple and quadruple therapy, respectively.

Overall, metformin was prescribed inappropriately (contraindicated and/ or inappropriate dosage) at admission and discharge in 93 patients (n=301, 30.9%) and 63 patients

(n=301, 20.9%) respectively. At admission, 65 patients (n=301, 21.6%) had at least one contraindication to the use of metformin, with the most common contraindication being cardiac failure (Table 7), whilst 42 patients (16.5%) were prescribed an excessive dosage at admission based on their renal function (Figure 4**Error! Reference source not found.**). Out of the 93 patients who were receiving metformin inappropriately at admission, in 53 patients (57%) metformin was continued at discharge despite a contraindication to its use or at an inappropriate dose. At discharge, 43 patients (n=301, 14.3%) had at least one contraindication and 21 patients (n=191, 11%) received an excessive dosage according to their renal function. In 47 elective surgical patients (from a total of 92 surgical patients), metformin was not ceased or re-started in accordance with guidelines in 19 (40.4%).

Table 7 Contraindications to the use of metformin at admission (n=301)

Contraindications		Patient number (%) [†]
Cardiac failure (moderate to severe)		18 (6.0)
Dehydration		2 (0.7)
Diabetic ketoacidosis		1 (0.3)
Gangrene		4 (1.3)
Liver dysfunction		14 (4.6)
Pancreatitis		5 (1.7)
Recent myocardial infarction		10 (3.3)
Renal dysfunction	CrCl (mL/min) <30	8 (2.6)
	eGFR (mL/min per 1.73 m ²) <30 [‡]	5 (1.7)
Respiratory failure		2 (0.7)

[†] Some patients had more than one contraindication to use metformin; [‡] Patients reported with eGFR are not including those reported with CrCl.

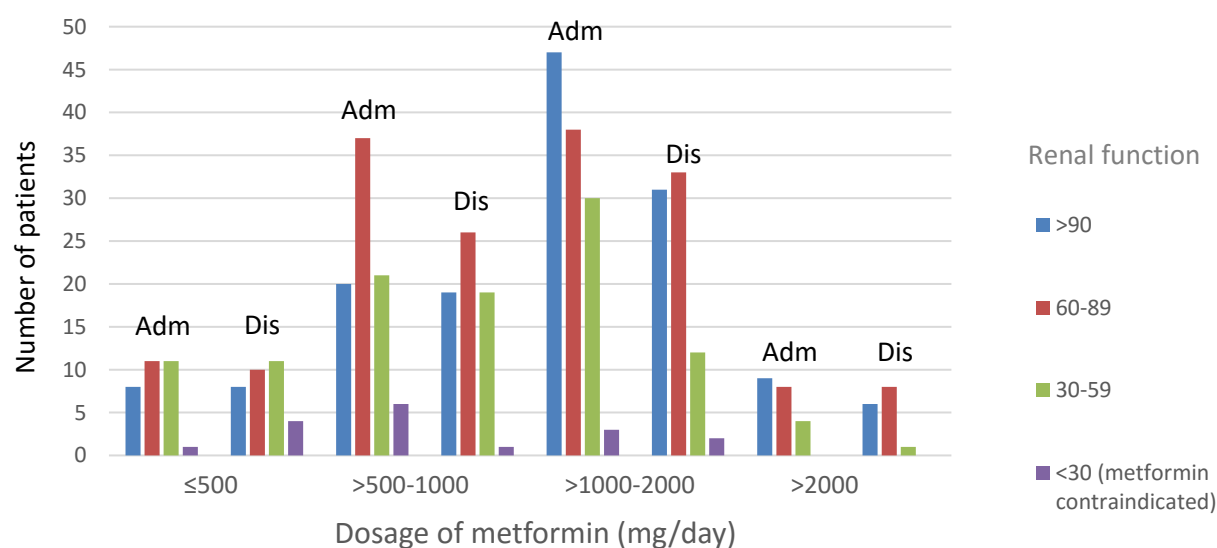


Figure 4 Distribution of patients based on different renal function (CrCl or eGFR) for different metformin dosages at admission (n=254) and discharge (n=191)

Adm = at admission; CrCl = creatinine clearance; Dis = at discharge; eGFR = estimated glomerular filtration rate; patient number with CrCl: at admission, n = 149; at discharge, n = 138; patient number with eGFR: at admission, n = 105; at discharge, n = 53.

The dosage of metformin could not be ascertained in some patients due to the missing documentation or inconsistent dosage recorded. For the T2DM patients with acute clinical condition, surgery or poor blood glucose controlled, insulin would be used during hospitalisation, and the dosage of metformin would be uncertain. We have used an additional method to identified AKI in case of missing documentation of AKI, with the consideration of eGFR and SCr levels of the patients'; however, AKI was being identified and documented clearly in the medical notes, there was no additional case of AKI which had to be identified.

Of 111 patients with a plasma lactate level and metformin dosage being reported at admission, 82 patients (n=111, 73.9%) had a value within the normal range (less than 2.4 mmol/L) and 25 patients (n=111, 22.5%) had a level between 2.4 and 5.0 mmol/L. Four patients had a plasma lactate level higher than 5.0 mmol/L and pH less than 7.35, but none of them had a recorded diagnosis of LA (Table 8). All 4 patients had at least one comorbidity (seizure, cardiac arrest or sepsis), that could have been associated with LA.³⁶ One patient (Patient 4,

Table 8) died within 24 hours after admission, with sepsis and non-ST segment myocardial infarction (NSTEMI) as the cause of death. The other three patients had their lactate level managed back to the normal range soon after admission. In all three patients, metformin was withheld during hospitalisation and re-commenced at discharge.

Table 8 Patients reported with increased lactate level

Patient no.	Age (years)	Gender	pH	Lactate (mmol/L)	SCr (μmol/L)	eGFR (mL/min per 1.73 m2)	Metformin at admission/discharge (mg/day)	Other conditions	Outcome
1	68	M	7.29	10.2	83	90	2000/1500	Seizure	Discharged
2	69	M	7.33	5.1	91	72	2000/2000	Ischaemic heart disease	Self-discharged
3	55	M	7.14	6.9	190	32	2000/1000	Cardiac arrest	Discharged
4	87	F	7.29	10.1	156	27	500 [†]	Sepsis, NSTEMI	Died

eGFR = estimated glomerular filtration rate; F = female; M = male; NSTEMI = non-ST segment myocardial infarction; SCr = serum creatinine; [†] Patient 4 died within 24 hours after admission.

2.4 Discussion

Approximately 31% and 21% of patients were prescribed metformin inappropriately at admission and discharge, respectively. There were 4 patients identified with LA according to biochemical definition in our study, but 3 patients survived after the emergency admission and were continued with metformin at discharge. The comorbidities in these cases were considered more likely to account for the occurrence of LA. Our finding of metformin often being prescribed in patients with contraindications to its use was reported in other studies.¹⁵¹⁻¹⁵⁴ The Fremantle Diabetes Study (FDS) in Western Australia found that 23.1% of patients receiving metformin had one or more contraindications to its use, and suggested that metformin did not increase the risk of LA.¹⁰⁸ They reported 3 confirmed cases of LA associated with metformin usage. Those three patients also had at least one significant comorbidity that could be associated with LA. Although the criteria included in the FDS were not exactly the same as this study, major contraindications to its use such as renal impairment and cardiac failure were included in both studies. The major contraindication was cardiac failure in our patients, while renal impairment was the main issue in the FDS.

The association between metformin and LA could be overemphasised. In addition, it has been reported that diabetes *per se*, rather than metformin therapy, was more likely to be the major risk factor in developing LA.¹⁵⁵⁻¹⁵⁷ Compared with non-diabetic patients, micro- or macrovascular disease in diabetic patients may also contribute to the development of acidosis, potentially by causing tissue hypoxia.¹⁵⁸

Metformin seems generally safe for use in most patients, even in those with contraindications. Scheen and Paquot¹³³ recently published a review suggesting that conditions such as mild-to-moderate chronic kidney disease and stable congestive heart failure should not be considered as contraindications to the usage of metformin. In our study, metformin was

continued at discharge despite a contraindication to its use, or at an inappropriate dose, in 57% patients who were prescribed the drug inappropriately at admission. These patients may have been admitted to the hospital because of reasons unrelated to diabetes. Doctors, understandably, might have been reluctant to make changes to the therapy if the patients' blood glucose levels were well controlled. A retrospective study in Canada found that 58 patients (28% of total) who were dispensed metformin had at least one contraindication, which included congestive heart failure, hepatic dysfunction and renal insufficiency; 50 of these 58 patients (86%) were continued on metformin after their contraindication(s) were identified.¹⁵⁹

Renal impairment is one of the major contraindications to the use of metformin as it is excreted unchanged through the kidney and could accumulate in renal impairment, thereby increasing the risk of LA.¹²⁶ In addition, lactate metabolism and excretion through the kidneys may be reduced in patients with renal impairment,¹¹⁵ further increasing the risk of LA. Although the AMH and guidelines in Australia do not have the same recommendation as the PI, that metformin should be avoided in CrCl less than 60 mL/min, dosage reduction according to renal function is recommended. LA may be more likely in patients with AKI, rather than chronic kidney disease.^{126, 160, 161} Patients with a diagnosis of AKI were not included in this study. Metformin was used in 13 patients with CrCl < 30 mL/min or eGFR < 30mL/min per 1.73m² at admission (Figure 4). One of these had a lactate level of 10.1 mmol/L (sepsis was more likely to be responsible in this case; Table 8).

Similar results were found in studies elsewhere^{162, 163} suggesting that metformin was frequently used in patients with renal impairment without developing LA. A cohort study on almost 52,000 T2DM patients in Sweden showed that metformin as monotherapy, compared to other oral anti-diabetic agents, was associated with a reduced risk of acidosis/ serious infection, and all-cause mortality in patients with an eGFR between 45 and 60 mL/min per

1.73m². Similar results were also seen in patients with an eGFR between 30 and 45 mL/min per 1.73 m².¹⁶⁴

Recent studies have suggested that metformin could be used safely in patients with renal impairment by controlling its plasma concentration and not exceeding 5 mg/L.^{165, 166} It was shown that the peak plasma metformin level would not exceed 5 mg/L in 95% of patients if the maximum daily dosage was restricted to 500, 1000, 2000 and 3000 mg in patients with CrCl of 15, 30, 60 and 120 mL/min, respectively. In addition, it was found that the plasma lactate did not have a significant correlation with either metformin plasma concentration or dosage.¹⁶⁶ However, clinical outcome studies regarding the safety of metformin in patients with renal impairment are lacking. It has been suggested that it would be more appropriate to adjust the dose of metformin according to renal function and monitor closely for any side effects rather than ceasing metformin therapy.¹⁶⁷

When interpreting the findings of this study some limitations should be considered. The retrospective nature of the study has rendered the data incomplete. We were only able to calculate CrCl in around half of the patients due to missing body weight, which might have led to inaccurate estimation of renal function. The eGFR levels were recorded from the laboratory results in the hospital and not adjusted to body surface area. In cases without complete documentation of a medical history, hepatic dysfunction and cardiac failure were identified according to their medications or pathology results. For example, patients in this study identified with having hepatic dysfunction may not necessarily have clinical hepatic dysfunction and the usage of metformin may still be appropriate. In addition, we were unable to identify the severity of hepatic dysfunction and it is important to note that severe hepatic dysfunction may still be a valid contraindication for the use metformin.¹³³ Similarly, we could not identify the severity of patients' cardiac failure. However, it is a standard approach to use the standard drug therapy for moderate to severe heart failure as an indicator, as these drugs

would not be used in combination for other indications.^{150 168} Given that recent clinical trials have shown benefits in patients with cardiovascular disease and cardiac failure,³⁹ it might be appropriate to continue metformin in patients who have well controlled cardiac failure rather than ceasing it.

2.5 Conclusion

Metformin was prescribed inappropriately in almost one third of the study patients, according to the current PI and guidelines. However, metformin appeared generally safe to be used in these patients, with no increased risk of acidosis. Cases of elevated lactate levels were identified, but these patients were also found to have other underlying clinical conditions associated with an increased risk of LA.

Together with previous findings, the evidence presented in this study suggests that the cautions/ contraindications stated in the PI and guidelines seem overly conservative including the attention on metformin-associated LA. Further clinical outcome studies in specific population groups are warranted to guide prescribers and the official PI should be reassessed and updated to reflect the current clinical practice. Thus, considerably more patients may be considered for treatment with metformin given its substantial benefits.

Chapter 3 Metformin utilisation in Australian community and aged care settings

3 Abstract

Objective: The objective of this study was to: i) evaluate the potentially inappropriate prescribing (PIP; defined as the use of metformin in the presence of contraindications and/or use in excessive dosage based on the renal function) of metformin in people receiving medication reviews in Australia; and ii) identify the predictors for PIP of metformin.

Method: Retrospective study of patients taking metformin through a large medication review database, containing records between January 2010 and June 2012. Data, including demographics, medical conditions, medications and relevant pathology results, were extracted for analysis. Multivariate logistic regression analysis was used to detect risk factors for PIP of metformin.

Results: Medication reviews pertaining to 6,386 patients who received Home Medicines Reviews (HMRs, n=5,327) or Residential Medication Management Reviews (RMMRs, n=1,059) were included in this study. Overall, there were 12.9% (n=685) of patients in the HMR group and 17.4% (n=184) of patients in the RMMR group who had PIP of metformin. Multivariate logistic regression showed age, gender and type of medication review service as the significant ($p<0.05$) independent risk factors for PIP of metformin.

Conclusion: Metformin was often used in patients with contraindications, or in higher than recommended dosages in patients with renal impairment. Given the recent debate in the literature about the role of metformin in the presence of contraindications, a detailed prospective study in patients with contraindications and its association with lactic acidosis is warranted to establish the way in which metformin is to be used in these patients.

3.1 Introduction

Metformin is a biguanide that acts as an insulin sensitiser and is commonly used in the treatment of type 2 diabetes mellitus (T2DM). Metformin is the first choice for the treatment of T2DM in the United States and Europe.⁴⁰ Similarly, the Therapeutic Guidelines in Australia¹⁶⁹ and by Diabetes Australia¹⁴² also recommend metformin as the first drug of choice for the treatment of T2DM. Patients taking metformin have a significantly reduced risk of myocardial infarction, as well as both diabetes-related and all-cause mortality.³⁷ Compared to most other medications used to treat T2DM, metformin does not cause weight gain, and is generally associated with a low risk of hypoglycaemia.⁴⁰

Despite the evidence-based benefits of metformin, concerns regarding the risks of lactic acidosis (LA) remain.¹⁴⁰ The mechanism of metformin-associated LA is complex and incompletely understood.¹²⁶ The clinical conditions that contraindicate metformin use are considered as risk factors for LA. For example, in patients with renal impairment, metformin may accumulate because the drug is mainly excreted by the kidney.^{115, 139} According to the Australian product information (PI; Glucophage®, Diabex® XR), metformin is also contraindicated in conditions that may be associated with tissue hypoxia, such as heart failure, respiratory failure, or pancreatitis.

Few studies internationally have recently questioned the contraindications to the use of metformin as it was not associated with a significant change in lactate levels compared to other antidiabetic agents.¹³³⁻¹³⁵ A recent study conducted in hospitalised patients reported that metformin was frequently prescribed despite the presence of contraindications.¹⁷⁰ However, data on the utilisation of metformin in Australian community and aged care settings is limited. Hence, the main objective of this study was to evaluate the use of metformin through a large sample of Home Medicines Review (HMR) and Residential Medication Management Review (RMMR) records in Australia, with a particular focus on assessing its use in patients with

apparent contraindications and in excessive dosage. The secondary objective was to identify the predictors for potentially inappropriate prescribing (PIP) of metformin (defined as the use of metformin in the presence of contraindications and or use in excessive dosage based on the renal function).

3.2 Methods

This retrospective study involved the collection of de-identified data from HMR and RMMR cases. These two Government-funded services represent a key strategy for achieving quality use of medicines in Australia. HMR is a community-based collaborative service provided by general practitioners (GPs) and accredited pharmacists. RMMR is available to all permanent residents of Australian Government-funded aged care homes.¹⁷¹ Both services comprise of: i) GP referral of a patient or resident; ii) accredited pharmacist visit (at home in the case of an HMR), including an interview of the patient or resident and review of medications to ascertain a comprehensive medication profile; iii) discussion by GP and pharmacist to develop a medication management plan based on findings and recommendations; and iv) consultation with the patient or resident to obtain agreement to the medication management plan.

Medscope™ is an IT company providing a decision support solution for accredited pharmacists performing medication reviews (HMRs and RMMRs). Approximately 15% of medication reviews in Australia are performed with the assistance of this online system which suggests that the sample would be likely to represent the population who receive medication reviews. The Medscope™ database contains approximately 40,000 medication review records for the period between January 2010 and June 2012. T2DM and metformin were the search terms used in identifying the patients to include in this study. All patients aged 18 years or more were included and no additional exclusion criteria was applied. Due to the de-identified

nature of the data collected, the study was exempted by the Tasmania Health and Medical Human Research Ethics Committee.

Patients' de-identified details, which included demographics, medical conditions, pathology test results and medications, were extracted. The medical conditions were coded according to the International Classification for Primary Care, second edition (ICPC-2), and all medications were coded according to the Anatomical Therapeutic Chemical Classification System.¹⁷²

Potentially inappropriate use of metformin was defined as having a contraindication to the use of metformin or an excessive dosage with respect to creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR). Renal function was determined by calculating the CrCl using the Cockcroft-Gault equation or the eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. In cases where CrCl could not be calculated (i.e. no documented body weight), the eGFR was used to identify PIP. We included moderate to severe heart failure, hepatic dysfunction, pancreatitis and renal failure (CrCl < 30 mL/min or eGFR < 30 mL/min per 1.73 m²) as contraindications.^{148, 173, 174} In the absence of a documented diagnosis, hepatic dysfunction¹⁴⁹ was defined as biochemical evidence of hypoalbuminaemia and abnormal serum levels of at least two of the following: total bilirubin, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase.

For the purpose of evaluating the inappropriate dosage of metformin taken in patients with renal impairment, the recommendations in Australian Medicines Handbook (AMH) were used.¹⁷⁴ The dosage of metformin conventional tablet was considered inappropriate in: i) a dosage higher than 3,000 mg per day in all the patients; ii) a dosage higher than 2,000 mg/day for patients with a CrCl 60-90 mL/min or an eGFR 60-90 mL/min per 1.73 m²; and iii) a dosage higher than 1,000 mg/day for patients with a CrCl 30-60 mL/min or an eGFR 30-60 mL/min per 1.73m². For patients taking metformin controlled-release tablets, it was considered

inappropriate in: i) a dosage higher than 2,000 mg per day; and ii) a dosage higher than 1,000 mg per day in patients with a CrCl 30-60 mL/min or an eGFR 30-60 mL/min per 1.73m². Potential under dosing of metformin was identified based on the documented glycated haemoglobin (HbA1c). Metformin was considered to be potentially under-dosed (prescribed less than its maximum dose with consideration of the renal function): i) if the patient's age was < 75 years and the HbA1c > 7.0% (53 mmol/mol), in the absence of any contraindications; or ii) if the patient's age was > 75 years and the HbA1c > 8.0% (64 mmol/mol),^{175, 176} in the absence of any contraindications.

The data were summarised and analysed using Microsoft Access 2010 and the IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY, US). Backward logistic regression analysis was used to identify the independent risk factors for PIP of metformin. Variables whose probability (p) values were ≤0.10 in the univariate analysis were entered into the logistic regression model. An alpha of <0.05 was used to test the statistical significance.

Backwards logistic regression was chosen as it starts with all potential predictors (significant in univariate analyses) included in the model and is a standard approach. Then it tests whether any of these predictors can be removed from the model without having a substantial effect on how well the model fits the observed data.

3.3 Results

A total of 6,386 patients were included in this study: 5,327 HMRs (49.2% male) and 1,059 RMMRs (39.1% male). The mean age of the patients was 69.7 ± 11.1 and 81.6 ± 8.3 years for HMRs and RMMRs, respectively (

Table 9). The majority of patients were older than 75 years (35.8% of HMRs and 79.9% RMMRs).

Table 9 Summary patient characteristics

		HMR (n = 5,327)	RMMR (n = 1,059)
Gender (male; %)		49.2 (n = 2,620)	39.1 (n = 414)
Age (mean ± SD; years)		69.7 ± 11.1 (n = 5,297)	81.6 ± 8.3 (n = 1,058)
	< 65 years (%)	30.0 (n=1,598)	3.4 (n=36)
	65 to < 75 years (%)	34.2 (n=1,824)	16.7 (n=177)
	≥ 75 years (%)	35.8 (n=1,905)	79.9 (n=846)
Weight (mean ± SD; kg)		90.3 ± 32.1 (n = 1,818)	72.9 ± 18.2 (n = 688)
BMI (mean ± SD)		33.09 ± 7.0 (n = 447)	30.0 ± 7.3 (n = 22)
HbA1c (%)		7.0 ± 1.4 (53 mmol/mol) (n=1,854)	6.8 ± 1.4 (51 mmol/mol) (n=222)
Dosage of metformin (mean ± SD; mg/day)			
	Metformin conventional tablet	1651.5 ± 735.6 (n=3,205)	1347.3 ± 650.8 (n=688)
	Metformin controlled release tablet	1214.5 ± 619.2 (n=2,055)	1060.3 ± 541.0 (n=369)
eGFR (mean ± SD; mL/min per 1.73 m ²)*		68.8 ± 20.2 (n = 1,624)	57.7 ± 20.9 (n = 225)
Stages of Chronic Kidney Disease	Stage 1: ≥ 90 mL/min per 1.73m ² (%)	18.0 (n=293)	8.0 (n=18)
	Stage 2: 60-89 mL/min per 1.73m ² (%)	46.6 (n=757)	32.9 (n=74)
	Stage 3a: 45-59 mL/min per 1.73m ² (%)	21.7 (n=353)	28.9 (n=65)
	Stage 3b: 30-44 mL/min per 1.73m ² (%)	12.0 (n=195)	23.1 (n=52)
	Stage 4: 15-29 mL/min per 1.73m ² (%)	1.6 (n=26)	7.1 (n=16)
	Stage 5: < 15 mL/min per 1.73m ² (%)	0	0
CrCl (mean ± SD; mL/min)†		73.0 ± 22.0 (n = 901)	52.9 ± 24.9 (n = 124)
Contraindications (%)		7.5 (n=398)	14.4 (n=152)
	Pancreatitis (%)	0.4 (n=22)	0.7 (n=7)
	Hepatic dysfunction (%)	0.2 (n=9)	0.2 (n=2)
	Heart failure (%)	6.4 (n=341)	11.7 (n=124)
	CrCl < 30mL/min or eGFR < 30mL/min/1.73m ² (%)	0.7 (n=39)	2.6 (n=28)
Inappropriate dosing (%)		20.2 (n=329/1,624)	20.0 (n=45/225)
Inappropriate prescribing (%)		12.9 (n=685)	17.4 (n=184)

*The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the classification is according to guideline of Kidney Health Australia; †The CrCl was calculated using the Cockcroft-Gault equation; BMI = body mass index; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; HbA1c =glycated haemoglobin; HMR =

Home Medicines Review; RMMR = Residential Medication Management Review; SD = standard deviation; T2DM = type 2 diabetes mellitus.

Overall, there were 12.9% (n=685) and 17.4% (n=184) of patients receiving HMR and RMMR, respectively, had PIP of metformin. There were 398 (n=5,327; 7.5%) patients in the HMR group and 152 (n=1,059; 14.4%) patients in the RMMR group who had at least one contraindication to the use of metformin. Heart failure was the most common contraindication in both groups. Based on renal function (either CrCl or eGFR), 329 patients (n=1,624; 20.2%) in the HMR group and 45 patients (n=225; 20.0%) in the RMMR group were taking an excessive dosage. In addition, 37 patients in the HMR group and 3 patients in the RMMR group were receiving metformin higher than the maximum daily dosage (more than 3,000 mg per day in conventional formula or 2,000 mg per day in extend-released formula). Potential under-dose of metformin was identified through the documented HbA1c in 49 patients in the HMR group (n=672; 7.3%) and 1 patient in the RMMR group (n=74; 1.3%).

Table 10 Association with PIP of metformin

Variables	p value
Age (years)	<0.01
Gender	0.06
Type of medication management*	0.02
Weight (kg)	0.28
HbA1c (%)	0.11

*Type of medication management: Home Medicines Reviews or Residential Medication Management Reviews

All study variables except for the ones used to define PIP of Metformin were entered in a backward logistic regression model. The backward logistic model proposed a three variables model after three steps removing weight and HbA1c status. Increasing age, female gender and patients living in residential aged care facilities (receiving RMMR) were more likely to be prescribed metformin inappropriately (Table 11Error! Reference source not

found., Both forward and backward logistic regression have been performed and no difference in the significance of results shows in these two regression models).

Table 11 Predictors for potential inappropriate prescribing of metformin from multivariate logistic regression analysis

	PIP of metformin Odds ratio (95% CI)	<i>p</i> value
Age	1.07 per year [1.04-1.09]	<0.01
Female	1.50 [1.05-2.14]	0.02
Patients receiving RMMRs	1.87 [1.10-3.18]	0.02

RMMR = Residential Medication Management Review

3.4 Discussion

Our finding of metformin often being prescribed in patients with contraindications to its use has been reported in overseas studies.^{153, 154} We previously found approximately one-quarter of patients admitted to hospital received metformin inappropriately with contraindications or in excessive dosage.¹⁷⁰ Emilie-Smith et al. reported 24.5% of people admitted to hospital receiving metformin had contraindications to its use.¹⁷⁷ Consistent with previous studies, heart failure was found as the most common contraindication in patients receiving metformin. Recent studies suggested that metformin may not be absolutely contraindicated and could be beneficial in these patients.^{97, 178, 179} A recent systematic review and meta-analysis suggested that in patients with comorbid heart failure and diabetes, metformin was the only anti-diabetic agent which has not been associated with harm.¹⁸⁰ It has also been suggested that physicians are increasingly disregarding the contraindications to metformin and the incidence of LA has not increased, so metformin may be safe even in patients with “contraindications”.^{137, 140}

Renal impairment is also one of the major contraindications to the use of metformin as it is excreted unchanged through the kidneys and could accumulate in renal impairment, thereby increasing the risk of LA.¹²⁶ However, metformin was found to be used commonly in patients with renal impairment,^{170, 181, 182} in both community and hospital settings. In our study

approximately 35% of the patients in the HMR group and 60% of the patients in the RMMR group were prescribed with metformin while having an eGFR < 60 mL/min per 1.73m². Of note that in 21.8% of patients in the HMR group and 27.1% of patients in the RMMR group were receiving metformin inappropriately based on their renal function.

The British National Institute for Health and Care Excellence (NICE) recently suggested that metformin can be used in patients with eGFR 45-60 mL/min per 1.73m².¹⁸³ The AMH recommends using metformin with dosage adjustment in patients with CrCl 30-90 mL/min and, while being contraindicated in patients with CrCl < 30 mL/min. Besides, Ekström and colleagues¹⁶⁴ evaluated the effectiveness and safety of metformin in more than 50,000 Swedish men and women with T2DM aged between 40 and 85 years, and found no increased risks of all-cause mortality, acidosis and/or serious infection, or cardiovascular disease in patients with eGFR 30-45 mL/min per 1.73m². It has been recently suggested that metformin may be tolerated at eGFR of < 30mL/min per 1.73m²,^{136, 184} particularly in patients with stable CKD with no other significant liver or respiratory disease, as CKD may not be a causative factor for LA but a co-precipitating factor.¹⁸⁴ Davoren recently proposed several changes to the current PI for metformin,¹³⁶ including: metformin might be used in selected patients with CrCl < 30 mL/min, where its use is closely supervised; and metformin could be continued despite some of the contraindications in the current PI, as long as the dose is reduced in these patients and stopped during acute illness.

The results from the logistic regression analysis showed that patients in the RMMR group were more likely to have PIP of metformin compared to the patients receiving HMRs. In this sub-analysis, more patients with heart failure and renal impairment in RMMR group were prescribed with metformin compared to those who received an HMR. In addition, older people were more likely to receive PIP of metformin. This is not surprising given that older people often suffer from multiple comorbidities and are likely to have more contraindications

to the use of metformin. However, many clinicians prefer using metformin in older people because of its benefits and also relatively low risk for hypoglycaemia.¹⁸⁵ The majority (approximately 80%) of patients in the RMMR group were ≥ 75 years. It is interesting to note that prior to 2010 the AMH recommended avoiding metformin in people aged greater than 85 years, but since then this recommendation has been revised to be used with caution. Similarly, the PI also recommends avoiding titration of metformin to its maximum dose in older people and avoiding use in people > 80 years unless normal renal function has been established. However, the literature on metformin usage in elderly is very limited, especially in people over 85 years. Future studies should evaluate in detail the benefits and safety of metformin in this age group.

It is interesting to note that in our study PIP of metformin was also identified in some patients in the absence of contraindications, i.e. prescribing of metformin beyond the maximal recommended dosage (3,000 mg per day) and potential under dose of metformin with respect to HbA1c. However, we did not have details of patients' compliance; making it hard to accurately establish the extent of under dosing of metformin based on HbA1c. Besides, the target of HbA1c varies depending on each individual, especially in elderly patients.

When interpreting the findings of this study some limitations should be considered. The data is incomplete due to the retrospective nature of this study. The sample in this present study represents the population with diabetes receiving these two services in Australia and may not represent the general population with diabetes. It is possible that patients referred for these services have more co-morbidities, multiple medications and are at a higher risk of drug-related problems compared to the general population with diabetes. In addition, we only included heart failure, hepatic dysfunction, pancreatitis and renal failure as contraindications to metformin.

From the database it was impossible to establish the severity of heart failure and our study may have overestimated the PIP of metformin with respect to moderate to severe heart failure. Furthermore, weight was not recorded in all patients and we therefore used the eGFR to identify PIP for patients in whom weight was not recorded. The interaction between variables included in the logistic regression model was not assessed in this study; therefore, for example, it is unknown whether the effect of age on the PIP of metformin is influenced by the gender. Although recent recommendations from the Food and Drug Administration and the National Institute of Diabetes and Digestive and Kidney Diseases suggest that eGFR can be used for drug dosing,^{186, 187} the AMH provides recommendations based on the CrCl as calculated by the Cockcroft-Gault equation.

3.5 Conclusion

Despite the limitations stated above, metformin was found to be often prescribed inappropriately; both in excessive dosage and in patients with contraindication(s). Currently, clinicians continue to prescribe metformin even in the presence of contraindications due to the substantial evidence of metformin benefit in patients with diabetes. However, given the recent debate in the literature about the role of metformin in the presence of contraindications a detailed prospective study in patients with contraindications in association with LA is warranted to establish the way in which metformin is to be used in these patients.

Part C

Chapter 4 Adverse event notifications implicating metformin with lactic acidosis in Australia

4 Abstract

Objective: To summarise the reported lactic acidosis cases associated with metformin from the Australian Therapeutic Goods Administration (TGA) and estimate the incidence of metformin-associated lactic acidosis (MALA) in Australia.

Method: All “lactic acidosis” cases associated with metformin and reported to the TGA between January 1971 and October 2014 were included. Data extracted included patient demographics, medical history and co-existing conditions, metformin dosage and relevant pathology results.

Result: A total of 152 cases of suspected MALA were included in this study. For 20 patients the outcome was unknown, and of the remaining 132 patients, 23 patients (17.4%) were reported as deceased. Plasma lactate levels were higher in non-survivors ($p=0.02$). Of 132 patients, 35 patients (26.5%) were reported to have at least one pre-existing contraindication to the use of metformin; this proportion was not different between patients who died or survived. Renal impairment was the most common contraindication. Approximately 75% of patients were reported to have at least one clinical condition which might cause acidosis. Metformin dosage, plasma lactate and serum creatinine were not correlated. Based on the cases reported to the TGA, the incidence of MALA in Australia was estimated to be 2.3 (95% CI, 1.5-3.1) cases per 100,000 patient-years between 1997 and 2011.

Conclusion: Pre-existing clinical conditions, such as renal impairment, and acute illnesses associated with lactic acidosis were frequently reported in the cases of MALA. The estimated

incidence of MALA was lower than in most previous studies in other countries, probably due to the nature of spontaneous reports to the TGA.

4.1 Introduction

Metformin is recommended as the first-choice for pharmacological treatment of type 2 diabetes mellitus (T2DM) in Australia⁹ and many other countries.^{40, 183} A wide array of benefits have been attributed to metformin. These include attenuation of abnormal glucose metabolism, weight loss, improvement in components of the metabolic syndrome, lipid lowering properties and cardiovascular protection.^{37, 184, 188, 189} A common clinical conundrum facing practitioners treating patients with T2DM is the potential risk of lactic acidosis (LA), which has a mortality rate of 30%-50%.^{190, 191} Metformin is implicated with type B₂ LA (a form of LA caused by drugs or toxins with no clinical evidence of insufficient tissue oxygen delivery) according to the Cohen and Woods (1976) classification. The incidence of metformin-associated lactic acidosis (MALA) has been estimated in the United States (US) and European countries,^{26, 108, 109, 192} but there is limited data in Australia. The reported incidence of MALA has varied, ranging from 1.5 to 530 cases per 100,000 patient-years; in comparison, LA has been reported with an incidence of 9.7 to 16.7 per 100,000 patient-years in individuals with diabetes not taking metformin.^{26, 107, 109, 111, 192, 193} Given the benefits of metformin and the relatively rare incidence of MALA, many recent publications have supported its expanded use, even in cases where it would be officially contraindicated, particularly as the available data suggest that lactate levels and the risk of LA do not differ appreciably in patients taking this drug versus other glucose-lowering agents.^{134, 135, 137, 140}

In Australia, adverse effect (AE) reporting is one of the main pathways for the Therapeutic Goods Administration (TGA) to monitor the safety of medicines. All reports are

analysed and checked by medical experts before becoming publicly accessible. These AE cases are reported mostly by pharmaceutical companies, as well as voluntarily by hospitals, general practitioners, State and Territory Health Departments, consumers and community pharmacists. The objective of this study was to: i) summarise the cases of LA related to metformin usage reported to the TGA and evaluate other medications and clinical conditions reported in these cases; and ii) estimate the incidence of MALA in Australia.

4.2 Methods

The terms “metformin” and “lactic acidosis” (defined by the Medical Dictionary for Regulatory Activities; MedDRA¹⁹⁴) were used to search the medication AE reports from the TGA. All cases reported from 1971 to October 2014 were obtained. There were no additional exclusion criteria applied in this study.

Data extracted included patient demographics, medical history including risk factors for LA, metformin daily dosage, other medications including documented therapy for acidosis (inotropes, mechanical ventilation and renal replacement therapy), relevant pathology results (e.g. lactate level, pH and creatinine) and description of the AE (the medical conditions or AEs were defined by MedDRA).

The medicines implicated in drug-induced LA were identified according to the Cohen and Woods classification type B₂.^{118, 121} The following medicines were included: isoniazid, linezolid, theophylline, valproate, spironolactone, beta-agonists, and anti-retroviral agents.

The data were summarised and analysed using Microsoft Access 2010 and the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, US). Independent t-tests or Mann-Whitney U tests were performed for comparing the continuous variables between

patients who died and survived. Spearman tests were used to explore the possible correlation between metformin daily dosage and plasma lactate level, plasma pH and serum creatinine. Pearson chi-square tests or Fisher's exact tests were performed for the categorical variables. An alpha of < 0.05 was considered statistically significant.

The estimated incidence of MALA was calculated using the average annual number of cases reported to the TGA from 1997 to 2011 (the annual numbers of community prescriptions of metformin reported in the Australian Statistics on Medicines were only available for this period), divided by the estimated annual number of patients taking metformin in these 15 years. The estimated patient number was calculated using the annual numbers of community prescriptions (i.e. subsidised and non-subsidised) of metformin reported in the Australian Statistics on Medicines¹⁹⁵ divided by twelve, assuming each patient had one prescription each month based on the standard dosage and pack quantities subsidised through the Australian Pharmaceutical Benefits Scheme.

4.3 Results

A total of 152 cases of LA potentially associated with metformin use were reported to the TGA during the study period [Due to the incomplete documentation in some of the case reports, the individual variable reported in the Results section were based on the actual available number of cases for each variable, number of patient (n) is not always equal to 152]. The median age of patients reported in the case reports was 68 years (IQR: 63-74 years, n=150 where age was documented) and 42.8% (n=152) were men. Patients had been treated with metformin in a mean (standard deviation, SD) daily dose of 2,124 (± 966) mg (n=134; six patients had a dose more than 3,000 mg per day, including intentional overdose). The mean lactate level was 12.0

(± 6.0) mmol/L, which was reported in 74 patients; the pH was reported in 51 cases (47 of these cases had noted lactate level).

The annual numbers of community prescriptions of metformin reported in the Australian Statistics on Medicines increased gradually from 1997 to 2011, while the reported number of MALA cases varied each year. Overall, the estimated incidence of MALA was 2.3 (95% CI, 1.5-3.1) cases per 100,000 patient-years (ranged between 0.5 and 6.8 cases per 100,000 patient-years) between 1997 and 2011.

For 20 patients the outcome was unknown. Table 12 shows the comparison between patients who survived and died. Of the 132 patients, 23 patients (17.4%) were reported as deceased. Plasma lactate levels were higher in patients who died ($p=0.02$, **Error! Reference source not found.**), but there was no significant difference found in age, plasma pH, serum creatinine or metformin daily dosage. Metformin daily dosage, plasma lactate, plasma pH and serum creatinine were not correlated, except for the plasma lactate and pH ($p<0.01$, Spearman $r=-0.66$).

Of the 132 cases, 35 cases (26.5%) were reported to have at least one contraindication to the use of metformin according to the medical history Table 12, and this proportion was not significantly different between patients who survived and died ($p=0.32$). Renal impairment was the most common contraindication.

Of the 132 cases, 98 cases (74.2%) reported at least one clinical condition which might cause acidosis (some cases had more than one condition, Table 12); acute renal failure (in 56 patients; $n=98$, 57.1%) was most common. Ten patients ($n=98$, 10.2%) had documented cardiac failure or circulatory collapse.

Of the 152 cases, 78 cases (51.3%) reported metformin as the only medication being taken. The most commonly prescribed anti-diabetic medications in addition to metformin were sulfonylureas (39.5%, Table 13). Ten medications associated with Type B₂ LA were identified in 29 cases (n=152, 19.1%; some cases had more than one medication associated with type B₂ LA). Four cases (n=152, 2.6%) reported metformin use with a contrast medium.

Table 12 Patient characteristics (survived vs non-survived)

	All patients (n=132)	Survived (n=109)	Non- survived (n=23)	p
Age (years)				
N	132	109	23	
Mean \pm SD	68 \pm 10	69 \pm 10	69 \pm 10	0.89 *
Median (IQR)	68 (63-76)	68 (63-75)	71 (63-78)	
Lactate (mmol/L)				
N	74	61	13	
Mean \pm SD	12.0 \pm 6.0	11.2 \pm 5.8	15.6 \pm 5.9	0.02
Median (IQR)	10.3 (7.7-16.5)	10.0 (6.6-16.2)	14.6 (10.1-20.0)	
pH				
N	51	42	9	
Mean \pm SD	7.0 \pm 0.2	7.1 \pm 0.2	6.9 \pm 0.2	0.07
Median (IQR)	7.1 (6.9-7.2)	7.1 (6.9-7.2)	6.8 (6.7-7.1)	
Serum creatinine (μmol/L)				
N	65	53	12	
Mean \pm SD	535 \pm 315	553 \pm 319	455 \pm 297	0.44
Median (IQR)	560 (223-735)	560 (230-730)	391 (199-782)	
Metformin daily dose (mg)				
N	118	96	22	
Mean \pm SD	2124 \pm 966	2130 \pm 932	2098 \pm 1126	0.91
Median (IQR)	2000 (1500-3000)	2000 (1500-3000)	2000 (1000-3000)	
Therapy				
Inotrope/Vasopressor (n; (%))	25 (18.9)	18 (16.5)	7 (30.4)	0.14 †
Renal replacement therapy (n; (%))	52 (39.4)	43 (39.4)	9 (39.1)	0.98
Ventilation/Intubation (n; (%))	9 (6.8)	8 (7.3)	1 (4.3)	1.00 †
Medical history				
Contraindication to use metformin (n; (%))	35 (26.5)	27 (24.8)	8 (34.8)	0.32
Heart failure (n; (%))	10 (7.6)	9 (8.3)	1 (4.3)	1.00 †
Renal impairment (n; (%))	27 (20.5)	21 (19.3)	6 (26.1)	0.56 †
Hepatic dysfunction (n; (%))	6 (4.5)	2 (1.8)	4 (17.4)	<0.01 †
Pancreatitis (n; (%))	1 (0.8)	1 (0.9)	0	1.00 †
Infection (n; (%))	10 (7.6)	9 (8.3)	1 (4.3)	1.00 †
Cancer (n; (%))	2 (1.5)	1 (0.9)	1 (4.3)	0.32 †
Adverse effect				
Patients had at least one of the following adverse effect documented (n; (%))	98 (74.2)	80 (73.4)	18 (78.3)	0.63
Cardiac failure/Circulatory collapse (n; (%))	10 (7.6)	5 (4.6)	5 (21.7)	0.01 †
Hepatic failure/hepatic function abnormal	3 (2.3)	1 (0.9)	2 (8.7)	0.08 †
Acute renal failure (n; (%))	56 (42.4)	45 (41.3)	11 (47.8)	0.56
Renal impairment (n; (%))	7 (5.3)	6 (5.5)	1 (4.3)	1.00 †
Dehydration (n; (%))	8 (6.1)	8 (7.3)	0	0.35 †
Respiratory function abnormal † (n; (%))	7 (5.3)	6 (5.5)	1 (4.3)	1.00 †
Anaemia (n; (%))	3 (2.3)	2 (1.8)	1 (4.3)	0.44 †
Cardiac/cardiopulmonary arrest (n; (%))	3 (2.3)	3 (2.8)	0	1.00 †
Seizure (n; (%))	2 (1.5)	1 (0.9)	1 (4.3)	0.32 †
Shock (n; (%))	6 (4.5)	3 (2.8)	3 (13.0)	0.06 †
Sepsis (n; (%))	6 (4.5)	4 (3.7)	2 (8.7)	0.28 †
Diarrhoea/nausea/vomiting (n; (%))	45 (34.1)	38 (34.9)	7 (30.4)	0.68

SD: standard deviation.

* Age was tested by independent t-test; lactate, plasma pH, creatinine and metformin dosage were tested using Mann-Whitney U test;

† The result from Fisher's exact test was reported; the others were presented with the result of the Pearson chi-square test;

‡ Respiratory function abnormal: included the description of respiratory impairment, respiratory disorder, exacerbation of asthma, respiratory distress, respiratory complication associated with lung cancer, respiratory failure.

Table 13 Medications usage in 152 patients

Medications		Number of patients (%)
Other anti-diabetic medications		
	One anti-diabetic medication in addition to metformin	63 (41.4)
	Two anti-diabetic medication in addition to metformin	11 (7.2)
	Insulin	18 (11.8)
	Sulfonylureas	60 (39.5)
	Thiazolidinediones	5 (3.3)
	DPP-4 inhibitors	1 (0.7)
	Exenatide	1 (0.7)
Medications associated with Type B₂ lactic acidosis		
	Isoniazid	1 (0.7)
	Linezolid	2 (1.3)
	Theophylline	1 (0.7)
	Valproate	2 (1.3)
	Spironolactone	8 (5.3)
β-agonist[‡]	Salbutamol	15 (9.9)
	Salmeterol	5 (3.3)
Anti-retroviral	Stavudine	1 (0.7)
	Didanosine	1 (0.7)
	Tenofovir	1 (0.7)

DPP-4 inhibitors: Dipeptidyl peptidase-4 inhibitors.

4.4 Discussion

The present study analysed a total of 152 LA cases associated with metformin usage from the national pharmacovigilance database in Australia. The mortality in this present study was approximately 17%, which was lower than reported rate in the previous literature.^{189, 196} It is possible that the severity of the cases was different (i.e. the plasma lactate levels in this present study were typically lower than in previous studies).¹⁹⁶⁻¹⁹⁸ For instance, Renda et al.¹⁹⁶ recently reported a mortality rate of 25.4% of MALA by reviewing the LA cases between 2001 and 2011 in the National Pharmacovigilance Network of the Italian Medicines Agency, noting a mean lactate level of 15.2 mmol/L in all the patients (vs. 12.0 mmol/L in this present study).

Kajbaf and Lalau reported the mortality rate associated with MALA fell steadily from around 50% to 25% since the 1960s, based on a worldwide pharmacovigilance database,¹¹³ suggesting that it might reflect the change in the outcome of systemic pathologies present in metformin-treated patients. The worldwide database used in their study included cases from different countries, in which adverse event reporting systems might be different; this may explain the difference of mortality rate from our estimation. Also, improvements in clinical management over the years might have been important in lowering the mortality.^{199, 200}

The cases of MALA in this present study frequently reported the presence of pre-existing contraindications and other risk factors of LA, so it might be true that metformin is often unfairly implicated as a cause of LA.²⁰¹ We observed more than one-quarter of patients had conditions contraindicating the use of metformin. Similar findings of metformin frequently being prescribed, disregarding the contraindications, have been reported.^{170, 177} The incidence of LA in patients receiving metformin with contraindications has apparently not increased.¹³³⁻¹³⁵ For instance, renal impairment may lead to the accumulation of metformin as it is excreted through the kidney. However, a recent cohort study of more than 77,000 patients with T2DM treated with metformin found that the incidence of LA did not differ from patients with or without renal impairment.²⁰² Besides, there was no correlation between the lactate level and the serum creatinine in our result.

Besides the pre-existing chronic medical conditions, most of MALA cases were complicated with acute medical conditions, which made it difficult to identify the cause of LA. Acute conditions including circulatory collapse, shock and sepsis were reported as AEs in approximately 75% of the cases, and these acute conditions are commonly associated with the risk of LA.^{122, 203} More than one-fifth of patients who died were reported to have cardiac failure or circulatory collapse. Underlying conditions such as circulatory failure, rather than metformin, have been suggested more likely to be the reason of LA.¹⁹³ Circulatory failure is one of the

most common causes of LA.^{118, 122} Acute kidney failure, found in more than 40% of patients in this study, may also contribute to the development of LA. According to the Cohen and Woods classification type B₁, acute kidney failure is associated with LA.¹¹⁸

Some medications should also be taken into consideration as a possible contributor in developing acidosis; these include valproate and anti-retroviral agents.^{121, 204} Cases of LA associated with medications, such as anti-retroviral agents and salbutamol, have been reported.²⁰⁵⁻²⁰⁷ Approximately 19% of the patients in this study received at least one other medication implicated in drug-induced LA according to the Cohen and Woods classification type B₂.^{118, 121} Notably, the co-medications that may trigger the occurrence of LA in cases associated with metformin were not often documented in previous studies of MALA cases.

It is often difficult to identify the contribution of metformin in LA cases due to the complexity in the acute condition (in presence with other co-existing conditions). Instead of “metformin-associated lactic acidosis”, the term “mixed lactic acidosis in metformin-treated patients” has been used, suggesting that “mixed” would better reflect the combination of other factors.¹¹³ Furthermore, it has been suggested that no consistent correlation between metformin serum level and LA has been established in previous studies.^{161, 208} In addition, we also found six patients noted with metformin overdose in this database. Metformin overdose (> 3,000 mg per day), may cause mitochondrial dysfunction and lactate overproduction.²⁰⁹ Cases of LA in metformin overdose have been reported previously.²¹⁰ with increased peak lactate level in most cases.

Our estimation of the incidence of LA cases associated with metformin in the community was 2.3 cases (ranged between 0.5 and 6.8 cases) per 100,000 patient-years, which might be an underestimation due to likely under-reporting of cases to the TGA. The published incidence of MALA has been estimated by two approaches: spontaneous reports to regulatory

agencies and pharmacoepidemiological studies in patients receiving metformin.²⁰¹ Compared to the incidence in pharmacoepidemiology studies, the estimated incidence from spontaneous reports is lower, as there is under-reporting due to unrecognised and unreported cases.²¹¹ Initially, the risk of MALA from the Food and Drug Administration following the approval of metformin in the US was reported at about 5 cases per 100,000 patient-years.¹¹¹ It is often agreed that the incidence of MALA using spontaneous adverse effect reports could be underestimated.^{201, 212}

When interpreting the findings of this study some limitations should be considered. The AE reports did not always have complete documentation in the database (e.g. the outcome was unknown in 20 patients.). Although the dosage of metformin was documented in most of the cases, the adherence to the treatment was unknown, as was serum metformin concentration. Hence, we were not able to establish the potential correlation between metformin level and LA, and also not able to conclude that the presence of LA was definitely induced by the use of metformin. The estimated patient number receiving metformin was calculated using the annual numbers of community prescriptions of metformin divided by twelve, with the assumption of each patient having one prescription per month, which may not reflect the real number of prescriptions in each patient individually. However, the annual number of prescriptions from Australian Statistics on Medicine is the best source to be used in estimating the community use of medication since it includes both subsidised and non-subsidised prescriptions.

4.5 Conclusion

The results showed that the other underlying clinical conditions or medications associated with risk of LA were frequently reported in MALA cases, which may also contribute to the severity of the illness. Metformin might be unfairly implicated as a cause of LA in cases with multiple

conditions. Our estimated incidence of MALA was lower than most of the previously reported values, probably because these AE cases were reported spontaneously. While ethically difficult, a detailed prospective study in patients with contraindications in association with LA is ideally warranted to establish the way in which metformin is to be used in these patients and also have a better understanding about the development of LA in metformin-treated patients.

Acknowledgement:

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Chapter 5 Lactic acidosis and the relationship with metformin usage: case reports

5 Abstract

Aims: The principal objective of this study was to retrospectively review a series of cases of lactic acidosis (LA) in patients with type 2 diabetes mellitus (T2DM) and examine the relationship with the use of metformin. More generally, the study enabled an investigation of the profiles of patients diagnosed with LA and clinical variables associated with in-hospital mortality.

Methods: All patients admitted to the Royal Hobart Hospital in Tasmania with LA (lactate > 5.0 mmol/L and pH <7.35) over a four-year period were included. Data extracted included patient demographics, medical history, medications, acute and chronic conditions associated with LA, and relevant pathology results. Multivariate logistic regression analysis was used to identify predictors for in-hospital mortality in patients with LA.

Results: A total of 139 patients with LA were included in this study. More than half (n=72, 51.8%) of the patients died during hospitalisation. Multivariate logistic regression revealed older age and lower pH as the significant independent predictors ($p<0.05$) for in-hospital mortality in patients with LA. A total of 23 patients had T2DM and 11 patients were taking metformin. All metformin-treated patients had at least one additional medical condition (either chronic or acute) associated with an increased risk for LA.

Conclusion: LA was associated with high in-hospital mortality, with older age and lower pH as the significant risk factors for mortality. In patients with LA, approximately half of the patients with T2DM were receiving metformin. All the patients treated with metformin had

other medical conditions which were risk factors for developing LA. The results support the “cautious expansion” of metformin use in patients with T2DM.

5.1 Introduction

Lactic acidosis (LA) is defined as a state of decreased systemic pH ($\text{pH} < 7.35$) and an elevated plasma lactate concentration ($> 5 \text{ mmol/L}$). It remains the most common cause of metabolic acidosis in hospitalised patients.²¹³ A recent review summarised the major causes of LA and the presumed mechanisms.¹²² Typically, LA is divided into disorders associated with tissue hypoxia (type A) and disorders in which tissue hypoxia is absent (type B). Type A LA may result from severe heart failure, sepsis, or cardiopulmonary arrest; type B can be caused by renal and hepatic failure, diabetes mellitus (DM) or drugs and toxins, including metformin, valproate and anti-retroviral agents.^{118, 121} It has been reported that cardiogenic or hypovolaemic shock, severe heart failure, trauma and sepsis were the most common causes of LA.²¹⁴

Lactate accumulation may be caused by increased production (i.e. increase glycolysis caused by hypoperfusion, hypoxaemia), decreased clearance (impaired hepatic metabolism or renal excretion), or a combination of both.¹¹⁴ The exact pathophysiology of elevated lactate is likely to be the result of more than one condition. Many studies have shown that high lactate levels are associated with increased mortality.^{122, 203, 215} The mortality rate of LA has been reported to be between 50% and 83%.²¹⁶⁻²¹⁸

DM has been also considered as one of the causes of LA.¹²² The possible explanations include: (i) LA in patients with diabetic ketoacidosis, which is likely to be due to hypovolaemia;¹²² or (ii) reduced activity of pyruvate dehydrogenase, which may cause increase lactate levels in patients with DM independent of ketoacidosis.¹⁵⁸ In addition, diabetic patients

with micro- or macrovascular disease are at an increased risk of LA, possibly due to the associated systemic hypoxia.¹⁵⁸ Furthermore, metformin, which is the first choice for the pharmacological treatment of type 2 diabetes mellitus (T2DM) in Australia⁹ and many other countries,^{33,219} has also been reported to be associated with LA. However, it has been suggested that the development of LA in metformin users was most likely due to the presence of concomitant risk factors,¹⁹³ rather than metformin alone. A causal link between metformin and LA is yet to be scientifically established.

Given this background, the principal objective of this study was to retrospectively review a series of cases of LA in patients with T2DM and examine the relationship with the use of metformin. More generally, the study investigated the profiles of patients diagnosed with LA and clinical variables associated with in-hospital mortality.

5.2 Methods

This retrospective audit included patients with a diagnosis of acidosis and who were admitted to the Royal Hobart Hospital (RHH), Tasmania between 1st January 2010 and 31st December 2013 (A four-year time frame was chosen based on practical reason, due to very low incidence of LA in metformin-treated patients and the difficulty in reviewing paper-based documentation.). RHH is the principal referral hospital in Tasmania; it has 500 beds serving around 250,000 people in southern Tasmania. Patients were included in the study if they were admitted for at least an overnight stay, aged 18 years and above, and noted to have acidosis (ICD10 E87.2) either at the time of admission or during their hospital stay. LA cases were identified as per documentation in the medical record and from the pathology results (lactate level > 5 mmol/L and a pH < 7.35 from the same sample). There were no additional exclusion criteria applied in this study.

For the purpose of this study, the maximum lactate value in each LA case was documented; and the pH value shown in the same test was reported. The LA cases associated with the usage of metformin were reviewed separately.

Other data extracted from patients' medical records included reason for admission, demographics, medical conditions (both chronic and acute), medications, and relevant pathology results (e.g. lactate, pH, bicarbonate, estimated glomerular filtration rate (eGFR), serum creatinine (SCr), albumin, total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT)).

For the purpose of this study, liver disease was defined either by documentation in the patient's medical history or by the presence of abnormal liver function tests (LFT), defined as hypoalbuminaemia and abnormal serum levels of at least two of the following (greater than the upper limit of normal): total bilirubin, ALT, ALP, and GGT. Acute kidney injury (AKI) was documented if noted in the patient's record during hospitalisation, or strongly suspected based on at least two increased SCr values.

All medicines potentially implicated in drug-induced LA were identified according to the Cohen and Woods classification type B₂, a form of LA caused by drugs or toxins with no clinical evidence of insufficient tissue oxygen delivery. The following medicines were included: metformin, isoniazid, linezolid, theophylline, valproate, spironolactone, beta-agonists, and nucleoside reverse transcriptase inhibitors.^{118, 121}

The data was summarised and analysed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, US). Descriptive statistics were used to describe the data. Chi-square or Fisher's exact tests were performed for the categorical variables. Independent t-tests were performed for comparing the continuous variables. Spearman tests were used to explore the possible correlation between age, lactate, pH, bicarbonate and eGFR.

Backward logistic regression was used to identify the independent risk factors for in-hospital mortality in patients with LA. Variables whose probability (p) values were ≤ 0.10 in the univariate analysis were entered into the final logistic regression model. A p value of <0.05 was considered statistically significant. The study was approved by the Tasmania Health and Medical Human Research Ethics Committee (Reference number: H0014090).

5.3 Results

Overall, 476 patients with acidosis during the study period were screened for inclusion. A total of 139 patients who met the definition of LA were included in the final analysis. Of 139 patients with LA included in this study (

Table 14), the mean age (SD) was 62 ± 18 years (range of 50 to 77 years) and 44.6% were female. The mean pH (SD) was 7.14 ± 0.15 , with a mean (SD) lactate level of 10.1 ± 4.8 mmol/L. Spearman tests revealed that an increased lactate level was correlated with decreased pH ($p < 0.01$, $r = -0.43$) and decreased bicarbonate ($p < 0.01$, $r = -0.58$).

Table 14 Number of patients with lactic acidosis

	All (N=139)	Survivor (N=67)	Non-survivor (N=72)	P
Gender (female; %)	62 (44.6)	27 (40.3)	35 (48.6)	0.41
Age (mean ± SD; years)	62 ± 18	56 ± 18	68 ± 17	<0.001
< 70	83 (59.7)	50 (74.6)	33 (45.8)	
70-79	30 (21.6)	9 (13.4)	21 (29.2)	
≥ 80	26 (18.7)	8 (11.9)	18 (25.0)	
pH (mean ± SD)	7.14 ± 0.15	7.18 ± 0.13	7.11 ± 0.16	<0.01
Lactate (mean ± SD; mmol/L)	10.1 ± 4.8	9.6 ± 5.0	10.6 ± 4.6	0.19
Bicarbonate (mmol/L)	15.1 ± 6.2	16.9 ± 6.1	13.4 ± 5.8	0.001
eGFR (mean ± SD; ml/min per 1.73m²)	45.3 ± 27.7	55.0 ± 30.8	36.0 ± 20.1	<0.001
Chronic medical conditions	N=131	N=62	N=69	
Patients have at least one chronic medical condition (n; %)	93 (71.0)	39 (62.9)	54 (78.3)	0.083
Asthma/COPD	25 (19.1)	12 (19.4)	13 (18.8)	1.00
Cancer	21 (16.0)	7 (11.3)	14 (20.3)	0.24
CKD	20 (15.3)	8 (12.9)	12 (17.4)	0.64
T2DM	23 (17.6)	12 (19.4)	11 (15.9)	0.78
Heart failure	15 (11.5)	6 (9.7)	9 (13.0)	0.74
Liver disease	52 (39.7)	20 (32.2)	32 (46.4)	0.14
Pancreatitis	6 (4.6)	2 (3.2)	4 (5.8)	0.68 *
Alcoholism	18 (12.9)	12 (17.9)	6 (8.3)	0.15
Acute medical conditions	N=139	N=67	N=72	
Patients have at least one acute medical condition (n; %)	118 (84.9)	54 (80.6)	64 (88.9)	0.26
Gastrointestinal symptoms	37 (26.6)	19 (28.4)	18 (25.0)	0.80
Seizure	11 (7.9)	8 (11.9)	3 (4.2)	0.17
Shock	19 (13.7)	5 (7.5)	14 (19.4)	0.07
AKI	44 (31.7)	18 (26.9)	26 (36.1)	0.32
Acute MI	7 (5.0)	3 (4.5)	4 (5.6)	1.00 *
Dehydration	7 (5.0)	4 (6.0)	3 (4.2)	0.71 *
Infection	26 (18.7)	10 (14.9)	16 (22.2)	0.38
Sepsis	40 (28.8)	13 (19.4)	27 (37.5)	0.03
Medications implicating type B₂ lactic acidosis (n; %)	N=110	N=56	N=54	
Patients have at least one medication associated with type B₂ lactic acidosis (n; %)	38 (34.5)	24 (42.9)	14 (25.9)	0.10
Metformin	11 (7.9)	6 (8.9)	5 (6.9)	0.90
Valproate	7 (6.4)	6 (10.7)	1 (1.9)	0.11 *
Spironolactone	3 (2.7)	3 (5.4)	0	0.24 *
Salbutamol	19 (17.3)	14 (25.0)	5 (9.3)	0.05
Salmeterol	9 (8.2)	6 (10.7)	3 (5.6)	0.49 *
Medications for T2DM (n; %)	N=139	N=67	N=72	
Insulin	6 (4.3)	5 (7.5)	1 (1.4)	0.11 *
Sulfonylureas	6 (4.3)	4 (6.0)	2 (2.8)	0.43 *
DPP-4 inhibitors	1 (0.7)	1 (1.5)	0	0.48 *
Treatment (n; %)	N=139	N=67	N=72	
Inotrope/vasopressor	39 (28.1)	14 (20.9)	25 (34.7)	0.10
Renal replacement therapy	37 (26.6)	14 (20.9)	24 (33.3)	0.15
Ventilation	36 (25.9)	16 (23.9)	20 (27.8)	0.74
Intubation	4 (2.9)	3 (4.5)	1 (1.4)	0.56 *

* Fisher's exact test was used. For other categorical parameters, chi-square tests were used to assess the association between the parameters and the clinical outcome.

AKI: acute kidney injury; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitors; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; LFT: liver function test; T2DM: type 2 diabetes mellitus.

Of the total 139 patients, the most common reasons for admission were: “diseases of the circulatory system” (n=36, 25.9%) and “diseases of the digestive system” (n=20, 14.4%). There were 131 patients with medical history documented, and the most common chronic medical condition associated with LA was liver disease (n=52, 39.7%), followed by asthma/chronic obstructive pulmonary disease (n=25, 19.1%). Of the 139 patients, 84.9% (n=118) had at least one acute medical condition associated with LA, with the most common being AKI (n=44, 31.7%), followed by sepsis (n=40, 28.8%). Of 110 patients with medications documented, over 30% of patients with LA were receiving medications (including metformin) associated with type B₂ LA.

Of the total 139 patients, more than half (n=72, 51.8%) of the patients who experienced LA died during hospitalisation. Compared to survivors, the patients who died were much older ($p<0.001$, Table 1), with over half of them older than 70 years. Univariate analysis to identify the risk factors associated with in-hospital mortality showed that age, pH, bicarbonate, eGFR and sepsis were all significant ($p\leq 0.10$). Multivariate logistic regression revealed two significant independent predictors for in-hospital mortality: aging increased the risk of mortality by 1.04 times for each additional year (95% CI 1.01-1.06, $p=0.003$), and a lower pH increased the risk of mortality by 25 times with each unit decrease in pH (95% CI 0.002-0.62, $p=0.02$).

Of the 131 patients with a medical history documented, 23 had T2DM, and 11 of these patients died. Approximately half (n=11) of the patients with T2DM were receiving metformin (eight patients were receiving metformin monotherapy;

Table 14). Of 11 metformin-treated patients, five of them died (45.5%) in the hospital; whilst in the non-metformin treated patients, six of them (50%) did not survive. There was no significant difference in either pH (7.13 ± 0.017 vs. 7.15 ± 0.11 , $p=0.79$) or lactate (10.2 ± 6.9 vs. 9.3 ± 3.5 mmol/L, $p=0.67$) between metformin users and non-users, respectively.

In patients receiving metformin, there were no patients with deliberate overdose, and metformin levels were not reported. Of the 11 metformin-treated patients (mean age of 74 ± 13 years), all patients had at least one medical condition (either chronic or acute) associated with an increased risk of LA. However, metformin was documented as the primary reason for the development of LA in four patients (patients 2, 5, 7 and 9 in Table 15). In all the other patients, sepsis was documented as the most common reason for LA. Five of the 11 patients died either at admission or during hospitalisation, with four of these aged 75 years or older. Among the patients who survived only one patient had a lactate level > 10 mmol/L (11.3 mmol/L). Metformin was re-introduced to all the survivors at discharge.

Table 15 Individual information of metformin users with lactic acidosis

Patient	Gender (M/F)	Age (years)	Days hospitalisation (days)	of Death	Dose of metformin (mg/day)	Glucose (mmol/L)	pH	Bicarbonate (mmol/L)	Lactate (mmol/L)	Serum creatinine (μ mol/L)	eGFR (ml/min per 1.73m ²)
1	M	74	60	No	1000	12.1	7.20	13	11.3	108	58
2	M	75	2	Yes	2000	14.2	6.92	2	29.0	538	8
3	M	42	22	Yes	N/A	8.0	7.06	14	5.2	183	38
4	M	79	4	Yes	N/A	11.0	7.06	12	12.8	86	74
5	F	81	6	No	1000	10.8	7.31	12	5.6	146	40
6	M	64	122	No	N/A	24.0	6.86	18	8.5	187	32
7	F	80	29	No	1000	11.6	7.19	11	6.1	148	29
8	M	84	31	No	1500	11.2	7.34	12	5.1	105	56
9	M	69	18	No	500	11.0	7.34	23	6.1	160	37
10	F	92	2	Yes	N/A	43.0	7.00	8	12.9	281	12
11	M	79	2	Yes	N/A	10.4	7.23	15	10.0	117	51

Continue of Table 15

Patient	Acute condition	Chronic condition (besides Type 2 DM)	Medications for T2DM	Other medication associated with type B ₂ lactic acidosis	Treatment for the acute illness	Reason of death
1	LFT abnormal	Alcoholic; colorectal cancer	Gliclazide	N/A	Inotrope, dialysis	N/A
2	AKI; GI symptoms; multi-organ failure	Metastatic bowel cancer	N/A	N/A	Inotrope	Ischemic small bowel; Multi-organ failure
3	GI symptoms; multi-organ failure; respiratory arrest; sepsis	CKD	N/A	N/A	Inotrope, dialysis	Sepsis caused multi-organ failure
4	GI symptoms; sepsis	Hypertension	N/A	N/A	Inotrope, dialysis	Ruptured abdominal aortic aneurysm
5	Septic shock	Hypertension; GORD; cataracts	N/A	N/A	N/A	N/A
6	Cardiac arrest; LFT abnormal	CKD; gout; hypertension, squamous cell carcinoma	Insulin	N/A	Inotrope	N/A
7	Acute MI; dehydration	CKD; depression; lupus	N/A	N/A	Ventilation	N/A
8	GI symptoms; sepsis	GORD; prostatic cancer	Glimepiride; sitagliptin	N/A	Vasopressor	N/A
9	Dehydration; hypotension; respiratory failure; right lower lobe pneumonia; sepsis	COPD; osteoarthritis	N/A	Salbutamol; Salmeterol	N/A	N/A
10	Acute MI; AKI; hypotension; HONK	Ischemic heart disease	N/A	N/A	Inotrope, intubation and ventilation	Acute MI
11	GI symptoms; haematuria	Depression; gout; hypertension; ischemic heart disease; squamous cell carcinoma	N/A	N/A	N/A	Sepsis secondary to aspiration pneumonia

AKI: acute kidney injury; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; GORD: gastro-oesophageal reflux disease; HF: heart failure; HONK: hyperosmolar non-ketotic acidosis; LFT: liver function test; MI: myocardial infarction; N/A: not available; SD: standard deviation; T2DM: type 2 diabetes mellitus.

5.4 Discussion

This study was designed to investigate the association between in-hospital mortality and multiple clinical factors in patients diagnosed with LA. LA was shown to result from various medical conditions, predisposing factors and medications. Despite appropriate management, the in-hospital mortality was high (approximately 50%). The most significant risk factors for in-hospital mortality were older age and lower pH.

The in-hospital mortality due to LA of 52% was within the range previously reported. The study by Scale and Harvey reported an in-hospital mortality rate of 54%, with an inclusion of a $\text{pH} \leq 7.2$, which was lower than that used in our study ($\text{pH} < 7.35$).¹⁵⁸ Also, consistent with their findings, this present study found no significant difference in lactate levels between patients who died and survived. In both the studies, most cases of LA resulting in-hospital mortality were complicated by other medical conditions, such as sepsis and AKI. AKI was reported in more than 30% of the cases, and was the most common acute condition associated with LA in our study. In our study, compared to survivors, the patients who died had a higher rate of sepsis ($p=0.03$), which has been identified as a common clinical condition associated with increased mortality in LA patients.²⁰³ Previous studies have demonstrated that mortality of LA cases is increased in patients with multiple comorbidities.^{122, 215}

A total of 23 patients with LA in our study were diabetic. DM, as well as metformin, is considered to be one of the causes of type B LA, but to date the exact mechanism of LA has not been elucidated. A study reported similar rates of LA in T2DM patients with and without metformin, and the authors suggested that LA in metformin users was likely related to the underlying medical conditions rather than the use of metformin alone.¹¹⁰ Furthermore, sulfonylureas have been suspected of LA with the incidence of LA approximately 4.8 cases per 100,000 person-years compared to 3.3 cases per 100,000 person-years among users of

metformin.²⁶ However, the incidence of LA in T2DM patients receiving other anti-diabetic medications is not yet well established.

In our study, 11 patients were receiving metformin either as monotherapy or in combination with other anti-diabetic medications. Five patients treated with metformin (45.5%) died, which was higher compared to a previous study conducted in Australia.²²⁰ That study retrospectively evaluated metformin-associated LA (MALA) cases in an intensive care unit over a five-year period, including patients with lactate levels > 2.0 mmol/L and pH < 7.30 . A total of 17 patients were diagnosed of MALA with an overall mortality rate of 29% (N=5). The severity of LA in our study may be different compared to that study, as we only included cases with a lactate level > 5.0 mmol/L. Furthermore, our patients receiving metformin were older (74 ± 13 years) compared to the study conducted in Adelaide (65 ± 10 years). Previous studies have reported that older age is associated with higher mortality in cases of MALA.^{158,}

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The safe use of metformin in patients with other chronic risk factors for developing LA is still under debate, especially in patients with CKD stage 3-5 (eGFR < 60 ml/min per 1.73m^2 , including patients on dialysis). Several studies have recently reported that metformin is a relatively safe option, including in patients with contraindications to its use, such as kidney disease.^{170, 177} Available data supports the “cautious expansion” of metformin use in T2DM patients with mild to moderate renal impairment.^{222, 223} However, a more careful approach is to be considered in patients who are at risk of abrupt worsening of renal function, especially in patients with CKD stage 3-4 (eGFR 15-59 ml/min per 1.73m^2), who may have serious clinical conditions predisposing to AKI.²²⁴

Furthermore, it is important to note that to date, no consistent link between LA and the use of metformin has been found.^{107, 158, 196, 220, 225} We were not able to identify the contribution

of metformin due to the other complications associated with LA in each case; besides, the metformin concentration was not measured in the hospital. Instead of “metformin-associated lactic acidosis”, a term “mixed lactic acidosis in metformin-treated patients” has been used.¹¹³ This may be more appropriate to describe the LA cases in metformin users (without metformin concentration measurement) who have other risk factors associated of LA.

This study has some limitations. The retrospective study design has resulted in missing or incomplete data. A cross sectional study design was used due to the very low annual incidence of LA cases in metformin-treated patients. Besides, it is difficult to match the LA cases and design a control group, as LA is an acute illness complicated by multiple medical conditions. The power of the study is low due to the small sample size. As the inconsistent documentation of cause of death in the hospital, and the association with multiple conditions of mortality in some patients, it was not always possible to summarise and report the reason for in-hospital mortality. We could not conduct any further investigation in the fatal cases to confirm the relationship with metformin use. Of 11 patients treated with metformin, the dosages were not documented in five patients.

5.5 Conclusion

LA was associated with high in-hospital mortality, with older age and lower pH as the significant risk factors for mortality. In patients with T2DM, approximately half of the patients were receiving metformin, and the mortality was similar between metformin users and non-users. All metformin-treated patients had other underlying medical conditions associated with the developing LA. The results support the “cautious expansion” of metformin use in patients with T2DM.

Part D

Chapter 6 Lactate levels in chronic metformin users: a narrative review

6 Abstract

Lactic acidosis (LA) cases had been reported in patients treated with metformin in two studies containing in Chapter 2 and 4; however, all the cases of metformin-associated lactic acidosis (MALA) reported in these two chapters were associated with other con-existing factors (i.e. acute illness, contraindications to the use of metformin). It was very difficult to identify the contribution of metformin in developing LA. Recently, more evidence from elsewhere suggested that metformin is generally safe to be used chronically in most patients. But it remains unclear whether metformin increases lactate levels chronically, as lactate level is not commonly measured in practice. The aim of this review was to summerise existing literature on the changes of lactate levels in chronic metformin users. The studies were subdivided into four themes summarising the lactate levels in metformin-treated patients, who (i) did not have contraindication to its use; (ii) had contraindication(s), especially in those have renal impairment; (iii) did physical exercise, which itself can raise lactate levels, at least acutely; (iv) received concomitant treatment with a nucleoside reverse transcriptase inhibitor (also known to have the ability to increase lactate levels).

6.1 Introduction

The potential risk of developing lactic acidosis (LA) is a major concern that has hindered the prescribing of metformin,^{222, 226} although metformin is one of the most widely used medications in the treatment of type 2 diabetes mellitus (T2DM) in practice. According to the official product information of metformin,^{84, 148} it is contraindicated in conditions including those with the potential to cause tissue hypoxia (i.e. cardiac failure, respiratory failure, sepsis) and those with the potential to alter renal function (i.e. dehydration, severe infection). As metformin is

mainly excreted through the kidneys unchanged, the official product information of manufacturer recommends avoiding use in patients with renal impairment (creatinine clearance (CrCl) $< 60 \text{ ml/min}$).⁸⁴ However, other sources, such as the Australian Medicines Handbook (AMH),¹⁰⁰ recommends avoiding metformin in patients with CrCl of less than 30 ml/min . It is important to note that the kidney also contributes to lactate metabolism and clearance, to the extent of 10-20%.¹¹⁵ In conditions where there is damage to the kidney, the elevation of lactate levels increases the risk of lactic acidosis. However, these warnings in the product information have been found to be increasingly disregarded in practice.^{153, 170, 177} Recently, metformin was reported as one of the most frequent prescribed anti-diabetic drug despite the presence of contraindications to its use.²²⁷ The occurrence of LA in metformin users is rare,^{26, 137} which has led to the debate that metformin is generally safe to use despite contraindications.¹³³

Studies have proposed several possible intracellular pathways likely to be involved in metformin increasing lactate production;^{55, 59} however, the exact mechanism is still not known. So far, it is not clear whether metformin increases lactate levels gradually throughout the treatment (non-acute condition), or whether the sudden rise in lactate level is triggered by a co-existing acute illness (acute condition).

Lactate level is not commonly being tested in clinical practice. In patients receiving metformin, lactate levels were mainly documented in individual or series of case reports of “metformin-associated lactic acidosis (MALA)”, an acute illness mostly occurring in the presence of other complications.¹⁹⁶ It was hard to identify if metformin was responsible for LA through these acute cases, as the complications may also be independently associated with the risk of developing LA. Limited studies published have reported lactate levels with continued metformin usage; therefore, it is not clear to what extent metformin would increase the lactate production with chronic regular use.

It is recommended that physical exercise and physical training would be beneficial in patients with T2DM.²²⁸ However, it has been suggested that lactate in patients with T2DM might not be metabolised so quickly compared to that in healthy subjects.²²⁹ Also, physical exercise can shortly and rapidly increase the lactate level,^{230, 231} which may particularly elevate the lactate levels in metformin-treated users. However, it is not clear to what extent lactate levels are affected in metformin users when they do exercise.

Nucleoside reverse transcriptase inhibitors (NRTIs), commonly used in treating patients with a diagnosis of human immunodeficiency virus (HIV), also have a side effect of developing LA.¹²² A systematic review identified that NRTI was one of the risk factors (the other one was female gender) for the development of LA in HIV infected patients.²³² Metformin has been introduced to patients who have had a diagnosis of human immunodeficiency virus (HIV), for its effect on improving insulin resistance and potential cardiovascular benefits.^{233, 234} Both agents are implicated with type B₂ LA according to the Cohen and Woods classification.^{118, 121 232} However, in practice, the changes in lactate levels in patients receiving both metformin and a NRTI are not clear.

Although metformin is commonly prescribed for patients with diabetes, it remains unclear whether the lactate level increases in chronic metformin users, and to what extent. This review examines lactate levels in chronic metformin-treated patients, including studies with the following conditions:

- Patients without contraindications to the use of metformin;
- Patients with contraindication(s) to the use of metformin, especially patients with renal impairment;
- Patients doing exercise;
- Patients who are HIV-positive and receiving NRTI therapy.

Whether monitoring lactate routinely would be useful is dependent on the findings of this review.

6.2 Methods

We searched the PubMed, Embase, Web of Science, Cochrane and International Pharmaceutical Abstracts databases covering the period up to 31 December 2015. Search terms included combinations of terms and key words, including “metformin”, “lactate”, “lactic acid” and “lactic acidosis”. Articles written in English were retrieved. The studies with an aim of reporting lactate levels in patients receiving metformin were included. Cases series of LA or MALA were excluded (blood/plasma sample: lactate > 5mmol/L and pH <7.35). Studies that included at least 10 patients taking metformin were included.

Titles and abstracts of the articles were screened to include relevant studies. In cases of insufficient information being ascertained from the title or abstract of a paper, a full copy of the article was obtained and screened to determine eligibility. Each article was evaluated for inclusion by the candidate (WH).

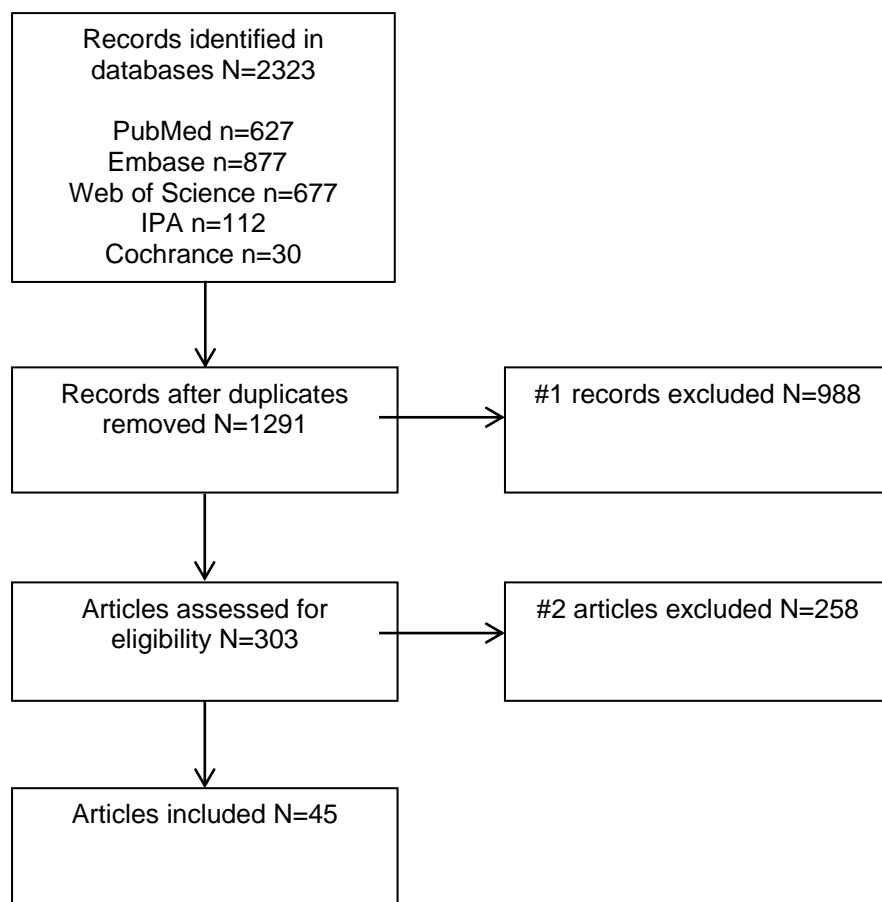
6.3 Results

A flow diagram of the literature search and identification of relevant articles for review is depicted in

Figure 5

Figure 5. Overall, 1,291 potentially relevant articles were identified. A total of 45 articles reported lactate levels in metformin users. The studies were subdivided into four themes as follows:

- Lactate levels and metformin usage in patients without contraindications;
- Lactate levels and metformin usage in patients with contraindication(s), or with renal impairment but without other contraindications;
- Lactate levels in patients taking metformin who exercise;
- Lactate levels in patients taking metformin who are HIV positive and receiving NRTI therapy.



#1

- Not relevant n=144
- reviews n=315
- Single case reports / Cases series <10 patients n=256
- Letter /Commentary n=95
- Animal / In vitro n=127

#2

- Lactate level not available n=120
- PK study n=15
- Subject matter not applicable n=68
- Case series of lactic acidosis or metformin-associate lactic acidosis n=55

Figure 5 Flowchart of study selection for this review

6.3.1 Lactate levels and metformin usage in patients without contraindications

Table 16 summarises the lactate level changes in the studies which excluded patients with any contraindications to the use of metformin or any comorbid conditions of diabetes. Most of these studies were conducted prospectively, and the lactate levels in metformin users were presented in comparison to the baseline level (before initiating metformin) or to the levels of non-metformin users (either receiving placebo or other diabetic medications). There were no cases of LA reported in any of these studies.

In the studies comparing lactate levels before and after the initiation of metformin therapy, most of the results showed slightly increased lactate levels in patients after the drug treatment, but the results were not statistically significant (Table 16). An early study published in 1996 reported slightly increased lactate levels in postprandial measurements ($p < 0.05$), after adding metformin (1,000 mg per day) to sulfonylurea therapy in 76 elderly patients, but not in the fasting state.²³⁵ Another study also reported lactate levels increased in patients after receiving metformin. That study was designed as a double-blind, cross-over clinical trial, testing two formulations containing different glibenclamide dosages in combination with metformin (800 mg per day initially, increased to 1,200 mg per day) in a total of 197 patients.²³⁶ The lactate levels in both groups with different medication sequences increased significantly compared to their baseline levels, but no clinically significant abnormalities were observed in either group.

Few studies have compared the lactate levels between metformin users and non-users. A study reported that postprandial lactate levels increased significantly in patients with T2DM and obesity, but the basal plasma lactate levels were not affected by metformin treatment.²³⁷ The authors considered the changes in lactate level were within the normal range and much less compared to the effects of exercise. The majority of studies monitoring lactate levels in metformin users without contraindications were conducted in the 1990s or even earlier. Most

of these studies were designed to investigate the therapeutic outcome and safety profile of metformin, and the results suggested that lactate levels remained the same after initiation of metformin treatment^{235, 238-243} or in comparison to non-metformin users.^{237, 244, 245}

Table 16 Studies without including patients with contraindications to metformin treatment

Reference: First author, year	Number of patients receiving metformin	Follow up	Lactate level of metformin users		Chronic medical conditions
			Compare to baseline	Compare to placebo/other diabetic treatment	
He 2012 ²⁴⁶	180	24 weeks		No difference (p=0.074)	Main exclusion criteria included: diabetes; known allergy or hypersensitivity to trial drugs; New York Heart Association grade II–IV heart failure, myocardial infarction or cerebrovascular accident in one year preceding the trial; acute infections; tumour; severe arrhythmia, mental disease, drug or alcohol abuse; history of hepatitis or cirrhosis or severe kidney disease; pregnant or lactating; or enrolled in other trials within the past 3 months.
Baradari 2011 ²⁴⁴	94	60 hours		No difference (p=0.793)	Patients were excluded due to liver disease, renal disease, heart failure, history of contrast or angiography within two days of surgery.
Iannello 2004 ²³⁸	20	10 days	No change*		Patients recruited comprised subjects with obesity or overweight or very mild diabetes, most often undiagnosed, who were observed in ambulatory or day-hospital for metabolic evaluation and dietary treatment. None of the subjects was taking medications of any kind nor had diabetic complications (ocular or renal) or other diseases.
Brunetti 2004 ²³⁶	197	6 months	Increase [†]		Patients were excluded due to severe diabetic complications (e.g. ketoacidosis, hyperosmolarity, severe infections); respiratory, cardiovascular (HYHA class III-IV), hepatic, or renal diseases, or pregnant, lactating or potentially child-bearing females.
Gregorio 1999 ²⁴⁷	89	18 months	Increase (fasting and average overall)*		Patients were excluded due to the contraindication to increasing sulphonylureas dose or adding metformin: alterations in liver function, severe macroangiopathy, respiratory or congestive heart failure, reduced renal function and excessive alcohol consumption.
Gregorio 1996 ²³⁵	76	12 months	No change (fasting)* Increase (postprandial) [†]		All patents had normal renal function and liver function test results; no severe macro-angiopathy or respiratory or congestive heart failure.
DeFronzo 1995 ⁴⁶	356	29 weeks	Increase*	Increase*	Patients were excluded if they had any of the following: symptomatic diabetes (polyuria, polydipsia, and weight loss), symptomatic cardiovascular disease, diastolic blood pressure above 100 mm Hg during antihypertensive-drug treatment, or any concurrent medical illness.

					Patients were also excluded if they had received insulin therapy within the previous six months, used medications known to affect glucose metabolism, consumed three or more alcoholic drinks per day (≥ 3 oz of alcohol per day), used illicit drugs, or had previously received metformin therapy.
Stumvoll 1995²³⁹	10	16 weeks	No change (fasting)*		Healthy obese patients with type 2 diabetes mellitus.
Campbell 1994²⁴⁰	24	52 weeks	No change (fasting)*		All patients were non ketotic, no evidence of cardiac failure, and with normal urea and electrolytes, creatinine and liver function tests. No alcoholic. None were taking steroids, salicylates, warfarin or monoamine oxidase inhibitors.
Yoa 1993²⁴⁸	10	4 weeks	Decrease (red blood cell) [‡]		10 Patients were healthy volunteers and the other 10 were newly diagnosed with type 2 diabetes mellitus.
DeFronzo 1991²⁴⁹	14	3 months	Increase *		Patients were diagnosed with type 2 diabetes mellitus: six with normal weight and 8 with obesity, but no major complication.
Pentikainen 1990²⁴¹	23	3 months	No change*		Patients were excluded due to renal or hepatic disease, heart failure, diabetes, body mass index > 40, pregnancy, use of drugs known to affect lipid levels, poor co-operation, and a high consumption of alcohol.
Gregorio 1990²⁴²	20	5 weeks	No change*		Patients had normal hepatic and renal functions and no evidence of vascular complications except for one patient with signs of initial and mild retinal microangiopathy.
Josephkuttty 1990²⁵⁰	20	12 weeks	Increase*		Patients were excluded due to abnormal blood urea, creatinine or liver function test and had a recent episode of cardiac failure.
Pedersen 1989²³⁷	10	4 weeks		No difference (fasting)* Increase (postprandial) [†]	The patients were obesity. None of the patients suffered from vascular complications or presented with biochemical evidence of abnormal hepatic or renal function.
Campbell 1987²⁴⁵	14	24 weeks		No difference (fasting)*	All patients were non-ketotic with had normal serum urea, electrolytes, and creatinine. None alcoholic or abnormal liver function test.
Marchetti 1987²⁵¹	13			Increase [†] compared to normal individuals	Patients had normal liver and renal function. The other medical conditions were not specified.
Pagano 1983²⁴³	14	4-6 weeks	No change*		Patients had normal liver and renal function. The other medical conditions were not specified.
De Silva 1979²⁵²	19	6 months		Increase [†] compared to	None of the subjects was taking any drugs and there was no evidence of hepatic or renal dysfunction or other endocrine

				treatment of clofibrate	disease.
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*result was not changed significantly; †p<0.05; ‡no p value reported.

6.3.2 Lactate levels and metformin usage in patients with contraindications

Metformin has been widely used in the presence of contraindications to its use.^{253, 254} In the studies included in this review, the reported changes in lactate levels were not consistent (Table 17).

A prospective cohort study reported increased mean lactate levels in 110 metformin users (as monotherapy or in combination with sulfonylureas or insulin);²⁵⁵ approximately 57% of the participants had elevated lactate levels after a follow-up period of two years. The patients included may have had other comorbidities, but they all had normal renal function. The mean lactate level in the high lactic acid group was 2.21 ± 0.57 mmol/L, with a range from 1.44 to 5.66 mmol/L; the detailed information of the cases with lactate higher than 5 mmol/L were not reported individually. The authors suggested that the duration of treatment with metformin (ranged from three to 36 months) did not seem to influence the plasma lactate levels. At the final evaluation of the study, high lactate levels were found in some of the patients, who were grouped separately from those with normal lactate. Compared to those with normal lactate, patients with high lactate levels had a higher ratio of complications, including congestive heart failure and infection. With the investigation of symptoms associated with high lactate levels and concurrent morbidities, the authors recommended metformin should be avoided in patients who had certain comorbidities (known to cause hypoxaemia or reduce tissue perfusion), particularly cardiovascular, respiratory or septic conditions that may enhance lactate production, and suggested that normal renal function did not protect patients from metformin-associated lactic acidaemia.

The authors of another prospective observational study has also suggested that metformin should be used with caution in patients with contraindications or stopped if there was evidence of acidosis.²⁵⁶ They considered lactate alone was insufficient to monitor effectively for the risk of LA in patients, whether they were metformin-treated or not. Their

results showed that metformin was associated with a small but significant increase in fasting plasma lactate levels in patients with T2DM compared to those treated with other medications (geometric mean [SD range]: 1.86 [1.34-2.59] mmol/L vs. 1.58 [1.09-2.30] mmol/L); both hyperglycaemia and being overweight were found to be associated with elevated plasma lactate levels. However, the patients treated with metformin had significantly longer durations of T2DM, greater BMI, higher pulse rate, fasting glucose, and haemoglobin A1c (HbA1c).

Different observations of lactate levels in metformin-treated patients were reported in other studies. A study reported lactate levels did not differ between the elderly (aged ≥ 80 years) and control groups (aged < 80 years) (approximately 1.46 ± 0.58 mmol/L and 1.50 ± 0.53 mmol/L, respectively).²⁵⁷ Patients with fasting plasma glucose levels > 7.2 mmol/L had a 2.8-fold increased risk of developing hyperlactaemia, but the authors stated that none of the cases fulfilled the LA criteria. Besides, the results showed that patients in the elderly group had a significantly lower daily metformin dose, higher creatinine levels, and lower estimated CrCl, compared with the control group (all $p < 0.05$). The increased lactate level was associated with decreased estimated CrCl in the elderly group ($p < 0.05$, $r = -0.27$), but not in the control group.

Besides, although increasing number of literature reports suggested metformin seemed generally safe to use in patients with T2DM, even in those with contraindication(s), whether to stop or continue metformin treatment in patients with contraindications is still under debate. A study recruited 393 metformin-treated patients, who were randomised to continue or to stop the drug.²⁵⁸ All the patients included had at least one contraindication to the use of metformin, with no differences in any of the baseline parameters between the two groups. After a follow-up of four years, the lactate levels were still similar in both groups (metformin continued vs. stopped). Besides, there was no difference between the two groups in the incidence of myocardial infarction, all cardiovascular events, or cardiovascular mortality. However, patients

who discontinued metformin had significant increase in weight ($p<0.002$) and HbA1c ($p<0.01$) compared to those who continued the drug. The mean serum creatinine (SCr) also rose gradually in both groups ($p<0.01$, initial vs. final values), but there were no significant differences between the groups. The authors suggested that patients with coronary heart disease, congestive heart failure and chronic obstructive pulmonary disease (COPD) had no reason to discontinue metformin treatment.

A recent retrospective study²⁵⁹ explored the safety of metformin in patients with T2DM who were admitted to the hospital with COPD exacerbation. The authors suggested that COPD should not present a barrier to the investigational or clinical use of metformin. The patients included in their study were at high risk of lactate accumulation: approximately three-quarters were hypoxaemic, over a third were in respiratory failure, and about a quarter had respiratory acidosis. Although the median lactate level was higher in metformin-treated patients compared to non-metformin treated patients, it remained in the normal range. In addition, they found that metformin treatment was associated with longer survival time in this population (5.2 years vs. 1.9 years, $p=0.011$), although further evidence is required to support these findings.

Table 17 Studies including patients with contraindications (in normal renal function).

Reference: First author, year	Number of patients (metformin users/total)	Follow up	Lactate (mmol/L)			Cases with lactate > 5 mmol/l and pH < 7.35	Study population	Chronic medical conditions (including comorbidities of diabetes mellitus)
			Metformin group	Comparison group	P value			
Duong 2015 ²⁶⁰	170	No	Indigenous: 1.55 (1.20-1.88); non-indigenous: 1.60 (1.35-2.10)	NA	NA	No	Patient with T2DM receiving metformin	Not specified
Hitching 2014 ²⁵⁹	51/130	For survival	1.45 (1.10-2.05)	1.10 (0.80-1.50)	0.012	No	Patients with COPD exacerbation with T2DM	Not specified
Morgana-Chaffin 2012 ²⁶¹	164/493	No (receiving medications 4-week prior enrolment)	1.00 (0.94-1.06)	0.93 (0.88-0.97)	<0.05	No	Patients with risk of atherosclerosis involved in Communities Carotid MRI study	Not specified
Lin 2010 ²⁵⁷	145 (aged ≥ 80 years, n=66 vs. < 80 years, n=79)	No	1.46 ± 0.58	1.50 ± 0.53	0.888	No	Patients with T2DM receiving metformin	No specified
Rachmani 2002 ²⁵⁸	195 (metformin continued) /393 (in total)	4 years	Initial 1.50	Initial 1.50	NA	No	Patient with T2DM receiving metformin and with the presence of at least one contraindication to metformin	Not specified
			Final 1.63	Final 1.66	NA			
Davis 2001 ²⁵⁶	181/272	1 year	1.86 (1.34-2.59)	1.58 (1.09-2.30)	<0.001	No	Patients involved in Fremantle Diabetes study	Not specified
Abbasi 2000 ²⁵⁵	110	2 years	Final assessment: Normal lactate group: 1.05 ± 0.19;	NA	NA	No	Patients with T2DM receiving metformin Normal serum creatinine (<132 µmol/L in men and	Not specified

			high lactate group: 2.21 ± 0.57 ($p < 0.001$)				<124 $\mu\text{mol/L}$ in women)	
Chalmer 1992²⁶²	70	No	Aged ≤ 65 years vs. aged > 65 years: 1.66 ± 0.58 vs. 1.53 ± 0.49 (p not available)	NA	NA	No	Patients with T2DM receiving metformin monotherapy or in combination with a sulfonylureas	Not specified
Waters 1978²⁶³	40/153	No	1.60 (0.2-4.2)	Sulfonylurea 1.16 (0.2-3.0)	<0.05	No	Patients with T2DM receiving metformin, phenformin or sulfonylureas; also patients on diet only.	Not specified

COPD: Chronic obstructive pulmonary disease; MRI: Magnetic resonance imaging; T2DM: type 2 diabetes mellitus.

6.3.2.1 Lactate levels and metformin usage in patients with renal impairment but without other contraindications

LA induced by metformin was very rare in patients with normal kidney function.^{106, 134, 258} The reduced renal function may lead to accumulation of metformin,^{74, 264} which would possibly leave patients at a higher risk of developing LA. In practice, there is no clear evidence to support whether to start or to continue metformin in patients with a CrCl between 30-60 ml/min. Some studies have reported measurement of lactate levels in patients with renal impairment without other comorbidities of DM or contraindication to metformin use (Table 18)

Studies reported that the mean fasting lactate levels showed no significant difference in different glomerular filtration rate (GFR) groups.^{265, 266} A study²⁶⁵ reported the mean fasting lactate levels in patients with T2DM treated with metformin in accordance to different renal function groups. The patients included were divided into three groups according to their GFR: < 60, 60-90, and > 90 ml/min per 1.73 m² (Table 18). The results showed no increase in fasting lactate levels in patients with GFR < 60 ml/min per 1.73m², and no significant difference in fasting plasma lactate of different metformin daily dosages. Results from another study,²⁶⁷ which included 24 elderly patients (70-88 years) with T2DM, showed that the mean lactate level remained unchanged in patients with CrCl > 60 ml/min receiving 1,700 mg of metformin daily over the two months of observation. Interestingly, for those patients with CrCl 30-60 ml/min, a lower dosage (850 mg per day) was given with a result of reduced mean lactate concentration compared to that of the baseline. In addition, there was no correlation between metformin levels and CrCl or between metformin levels and lactate levels reported in this study.

However, another two studies elsewhere reported positive correlations between fasting lactate level and SCr. The two studies, which did not include patients with renal impairment,

showed that the GFR in some of the patients were lower than 60 ml/min per 1.73m² despite a SCr within the normal range.^{268, 269} In both studies, all the patients were treated with metformin 1,500 mg daily for at least one week, and the reported mean lactate levels in metformin users were significantly higher than those of non-users; however, the lactate levels were still within the normal range.

A study²⁷⁰ evaluated the risk of LA and hypoglycaemia in 35 patients with end-stage kidney disease (ESKD) and T2DM who were receiving automated peritoneal dialysis therapy. They initiated metformin treatment in patients without other risk factors of LA. Although 85% of their patients had a moderate or markedly raised metformin concentration, the mean lactate level was 1.39±0.61 mmol/L, and hyperlactatemia (> 2 mmol/L to 5 mmol/L) was found in only 4/525 plasma samples, but no patients had a plasma lactate level above 5 mmol/L. Besides, no correlation was established from the results between the levels of plasma metformin and lactate. The authors suggested the increased lactate was not necessarily a result of metformin accumulation.

Table 18 Studies including patients with renal impairment

Reference: First author, year	Num. of patients	Renal function		Lactate in metformin users (mmol/L)		Case of hyperlactaemia/ lactic acidosis	Comment
				In different stage of renal function	Mean		
Al-Hwiesh, 2013 ²⁷⁰	35	End-stage renal disease			1.39 ± 0.61	4/525 blood sample with lactate > 2 mmol/L (but <5 mmol/L)	Excluded patients with additional risk for lactic acidosis
Shen, 2013 ²⁶⁸	392	Slightly impaired renal function			1.26 ± 0.43		Excluded all patients with additional risk for lactic acidosis
Liu, 2009 ²⁶⁹	1,024	GFR (ml/min per1.73m ²)	<60	1.13 ± 0.47	1.32 ± 0.52	62/1024 patients with lactate > 2mmol/L	Excluded patients with additional risk for lactic acidosis
			61-90	1.23 ± 0.50			
			≥91	1.21 ± 0.49			
Lim, 2007 ²⁶⁵	97	GFR (ml/min per1.73m ²)	<60	1.7 ± 0.3		20 patients with lactate >2.2mmol/L; 1 patients with lactate >5.0 mmol/L, but not satisfy the criteria of lactic acidosis	Excluded patients with additional risk for lactic acidosis
			60-90	1.8 ± 0.3			
			>90	1.8 ± 0.4			
Connolly, 1996 ²⁶⁶	42	SCr (µmol/L)	>120	2.3 ± 0.8		No	Excluded patients with additional risk for lactic acidosis
			<120	2.64 ± 1.4			
Lalau, 1990 ²⁶⁷	24	CrCl (ml/min) after 2 months	>60	1.48 ± 0.18		No	Patients were free from cardiovascular complications and had normal hepatic function.

6.3.3 Lactate levels in patients taking metformin who exercise

To date, the tested intensity of exercise in patients with T2DM was moderate in most studies. A recent study investigated the role of metformin on glucose kinetics during moderate exercise (60% $\text{VO}_{2\text{max}}$ for 45 minutes).²⁷¹ The results showed that mean plasma lactate concentrations were significantly higher during and after exercise, as well as during recovery, in all patients in the T2DM group compared to those of subjects in the healthy control group; whilst patients with T2DM receiving metformin had significantly higher mean lactate levels in recovery compared to the levels in healthy control group. The authors suggested that the elevated plasma lactate concentrations in patients with T2DM was not an unexpected finding in hyperglycaemic patients, since an enhanced glycolysis rate in skeletal muscle was observed in their results. The lactate recoveries were similar between patients with T2DM treated and un-treated with metformin. The authors concluded that metformin as well as exercise could be undertaken in combination in patients with T2DM, as the results suggested that the increasing lactate levels were more likely related to the exercise rather than metformin.

Another study²⁷² also found that lactate concentrations were significantly higher in the metformin-treated group at recovery compared to the glibenclamide-treated or healthy control groups. The intensity of exercise used in this study was also moderate (50% $\text{VO}_{2\text{max}}$ for 45 minutes). The authors suggested that the higher lactate in the metformin-treated group may be due to the interference with lactate clearance.

However, the observations from other studies revealed little or no difference in lactate levels during exercise in patients with T2DM receiving metformin.^{273, 274} One of the studies²⁷³ reported that maximal plasma lactate levels or mean plasma lactate levels during exercise did not correlate with the metformin plasma concentration. The study also reported that the plasma lactate concentration fell more slowly following metformin administration than after placebo, or after conclusion of the exercise.

A study conducted in Canada²⁷⁵ determined the effect of metformin in response to submaximal exercise. The initial exercise intensity used in this study was mild and increased gradually, which was a combination of 30% $\text{VO}_{2\text{max}}$ for 15 minutes, 60% of $\text{VO}_{2\text{max}}$ for 15 minutes and 80% $\text{VO}_{2\text{max}}$ for 5 minutes. Elevated lactate levels were reported in metformin-treated patients compared to patients receiving placebo.²⁷⁵ High intensity training could be dangerous if there were any disease-related limitations of the cardiopulmonary system.²²⁹

6.3.4 Lactate levels in patients taking metformin who are HIV positive and receiving NRTI therapy

Due to a potential mitochondrial toxicity resulting from the interference with oxidative phosphorylation from NRTIs, there is a potential risk associated with increased lactate levels in HIV-positive patients who were treated with a NRTI. A prospective, randomised, double-blind, placebo-controlled study compared the effects on body fat after 1 year of therapy with either gemfibrozil (1,200 mg per day) or metformin (1,700 mg per day) in HIV-infected patients on protease inhibitor-containing highly active antiretroviral therapy.²⁷⁶ The results showed no significant changes in plasma lactate levels in all the study groups. Results from another two studies for shorter treatment durations (three months in each study) also showed that both low dose (1,000 mg per day) or moderate dose (1,700 mg per day) metformin did not influence the lactate levels.^{234, 277} One of these two studies²⁷⁷ demonstrated that a combination of metformin and exercise improved cardiovascular and biochemical parameters significantly more than in patients receiving metformin alone. But the results in both studies may have to be interpreted with caution since the sample sizes were small and strict eligibility criteria precluded participation of patients with known contraindications (i.e. liver or kidney disease).

6.4 General discussion

In patients without any contraindications listed in the official product information, metformin is the first-line oral therapy for patients with a diagnosis of T2DM. Although an increasing number of literature reports showed that metformin was prescribed in patients with contraindications to its use, the incidence of LA did not seem to increase.^{26, 278} In this review, the reported lactate levels varied among different studies. Although some studies reported significantly increased lactate levels in metformin-treated patients compared to the baseline (before initiating metformin) or non-metformin users, the lactate levels mostly remained in the normal range.

In balance the benefits and risk of metformin therapy, conditions including stable coronary artery disease, acute coronary syndrome, and stable congestive heart failure should not be considered as absolute contraindications to the use of metformin in patients with T2DM.¹³³ In addition, CKD, with appropriate dosage reduction of the drug, should not be considered an absolute contraindication to the use of metformin. Thus, recent data and reviews have suggested no increase in the incidence of LA in the increased metformin users with diminished renal function.^{26, 133, 270} Most recently, the United States Food and Drug Administration (FDA) announced that metformin can be used safely in patients with mild and, in some with moderate kidney impairment. With the latest recommendation from FDA, a patient's eGFR should be obtained before initiating metformin and the drug is not recommended to start in those with an eGFR between 30-45 ml/min per 1.73m².²⁷⁹ Besides, for patients whose eGFR declines to 30-45 ml/min per 1.73m² during the treatment, the risk and benefits should be assessed before continuing metformin.

The debate remains as to whether metformin could be started/ continued in patients with an eGFR of 30-45 ml/min per 1.73m²,^{280, 281} mainly because there is a potential risk of developing acute kidney injury (AKI) in patients with CKD;^{282, 283} In case of unstable renal

function, metformin is recommended to be stopped immediately in any acute events which may rapidly cause renal function deterioration or trigger the development of LA, including dehydration, gastrointestinal disorders and infectious disease.^{133, 184, 284, 285}

AKI was not the only acute condition associated with increasing risk of LA, the other acute illness, which may be related to pre-existing comorbidities in metformin-treated patients, would trigger a sudden large rise in lactate level.^{280, 286} Cautions of using metformin remained in certain conditions such as worsening cardiac failure or myocardial infarction, respiratory failure, shock, significant blood loss, sepsis, gangrene and pancreatitis.²⁸⁷ These acute conditions could potentially increase lactate levels and lead to LA, and metformin should be ceased temporarily or withdrawn.²⁸⁷

Almost all the MALA cases reported in clinical trials or cases series occurred with pre-existing comorbidities, including acute medical conditions (i.e. sepsis, infection).^{104, 196} Regular lactate level monitoring in metformin-treated patients may not be able to predict the sudden changes if LA develops acutely. In 2010, the Japanese Ministry of Health, Labour and Welfare approved a metformin formulation which allowed a maximum dosage to increase to 2,250 mg per day.²⁸⁸ One year after the new regulation was authorised, a caution was added in the Japanese metformin product information to give a warning regarding the risk of MALA following dehydration, and to recommend renal function testing for the patients at risk, including the elderly (aged 75 years or older).²⁸⁹ A study reported²⁸⁸ that the number of lactate measurements increased after the regulatory action, but the prescription of metformin to elderly patients and overall users stayed constant during the study period (from April 2011 to March 2013). The authors suggested that doctors considered the benefits of metformin treatment administrated under conditions of careful lactate monitoring to outweigh the risk of LA. However, the study did not report the incidence of LA in metformin users after the regulation and caution being advised.

It is still not clear if regularly monitoring lactate levels in metformin users could be helpful in minimising the incidence of LA. So far, no consistent association has been established between lactate level and metformin concentration or its dose. Since the incidence of LA in metformin users remains low, a regular lactate level test may become an extra burden to patients and waste of health care resources.

In metformin-treated patients with T2DM, it is not easy to prove how training-induced alteration affect the lactate levels. In this review, the results varied in the included studies, which were mostly in design of moderate intensity exercise. Brinkman summarised that various factors, which have been suggested in different studies, could affect the lactate levels.²²⁹ Physical training could counteract a diminished oxidative capacity (by increasing the aerobic-oxidative capacity in patients with T2DM by raising skeletal muscle mitochondrial density,²⁹⁰ capillary supply²⁹¹ and oxidative gene expression²⁹²), which has been considered to be the major cause of elevated lactate. Besides, physical training may improve lactate transport and clearance.²²⁹ The information for metformin users who combined exercise to control their diabetes is still limited; besides, patients with other medical complications (i.e. diabetes-related complications, hepatic dysfunction) were normally excluded. Future studies on patients with other comorbidities, combining medication treatment and different intensities of physical training, are warranted.

Similarly, only few studies have been conducted to test the lactate levels in NRTI-treated patients who were receiving metformin, and the sample sizes were small. According to the summary of available studies, the lactate levels were not being influenced by these two mediations. More studies are required to establish the safe use of metformin in patients also receiving NRTI therapy, including dosage recommendations.

There are some limitations in this review. Limited studies reported regular lactate levels in non-acute conditions, and the majority of these studies were limited by small sample size. Besides, most of the studies included in this review were in cross sectional or case-control study design. The prospective studies were mostly designed with selective populations, with an exclusion of patients with contraindications to the use metformin or any comorbidities. However, in practice, patients with diabetes have increased risk of cardiovascular comorbidities and other complications such as CKD, which are often conditions that may be associated with risk of increasing lactate levels. Due to the heterogeneity of the studies, it is not feasible to perform a meta-analysis. Therefore, no definite conclusions on the benefits of regular lactate monitoring in metformin users can be made.

6.5 Conclusion

Studies have reported that treatment with metformin could increase lactate levels compared to that of non-metformin users. However, most results showed that the lactate level remained in the normal range, which made metformin a good choice in the treatment of T2DM. In patients with so-called “contraindications” or unstable medical conditions, regular lactate level tests in metformin users may have a potential to capture elevated lactate level earlier and withdraw the drug treatment; however, this has not yet been proved. Future research on larger populations focusing on measurement of lactate levels in continuous metformin users are warranted.

Part E

Chapter 7 Discussion and Conclusion

The current PI of metformin persists with advising extreme caution for its use, especially in fears of the risk of LA. The studies outlined in this thesis were conducted using Australian data to evaluate the prescribing adherence of metformin to the PI and therapeutic guidelines, explore LA cases that occurred in patients treated with this drug, and summarise the changes recorded in lactate levels in chronic users. In total, four original research studies and one review were conducted to achieve this aim.

The strict adherence with the PI was often being disregarded. The review of digital medical records of patients admitted to RHH (Chapter 2) found that more than 30% of patients were receiving metformin inappropriately (i.e. in present of contraindications or excessive dosage). Surprisingly, more than 50% of the patients who were receiving metformin inappropriately at admission continued the inappropriate use at discharge, even in the small set of survivors who had LA. Inappropriate prescribing of metformin was also common in patients living in the community and aged care facilities who received either an HMR or RMMR (0). Approximately 13% of patients receiving HMR and 17% of RMMR were receiving metformin inappropriately. Heart failure was found to be the most common contraindication in both studies (Chapter 2 & 0). Emerging evidence suggested metformin may have benefits in lowering the incidence of myocardial infarction, improving morbidity and mortality in patients with heart failure and cardiac disease, and potential protective effect against ischaemic injury.^{39, 133, 293} It has been suggested that the contraindication in prescribing metformin in patients with heart failure are too strict, as increasing evidence supported that the drug could be used safely in this population.^{39, 133, 136, 293, 294} In patients with heart failure or cardiac disease (of stable condition), metformin could be used with caution.

The patients included in both studies (Chapter 2 & 0) were mostly elderly: (i) the mean age of patients receiving metformin who admitted to the RHH was 68 years; (ii) in the study of patients receiving HMR or RMMR, the mean ages were 70 and 82 years respectively, and older age was a predictor of inappropriate prescribing of metformin according to the logistic regression analysis (with female gender and patients receiving RMMR as the independent predictors). Recently published studies reviewing medication usage in the elderly outside of Australia also reported that metformin was one of the most common inappropriately prescribed medications.^{253, 254, 295} Elderly patients generally have multiple comorbidities, which can easily complicated or contraindicated to the use of metformin. It has been suggested that elderly patients with diabetes have a higher risk of both microvascular and cardiovascular diseases, geriatric conditions (eg. falls, dementia), and hypoglycaemia compared to non-diabetic subjects.²⁹⁶ Among the commonly used anti-diabetic medications (i.e. insulin, sulfonylureas), metformin is less likely to cause hypoglycaemia, which may be beneficial in elderly.

The current AMH (2016) suggests using metformin cautiously in elderly with reduced dosage and renal function monitoring, although it was previously recommended to avoid the usage in very old people (i.e. > 85 years).²⁹⁷ There are concerns of prescribing metformin in geriatrics, as the number of comorbidities increases with age. The underlying medical conditions may further increase the risk of lactate elevation (i.e. renal function decreases in aging population). However, the usage of metformin in elderly patients has increased over the years. A population-based cohort of patients aged 80 years or older with diabetes reported that the mainstay of antidiabetic therapy had changed from sulfonylureas (94% to 29%) to metformin (22% to 86%) from early 1990s to 2010s.²⁹⁵

Metformin has also been reported to be underutilised in patients with diabetes. Potential under dose of metformin was identified in some patients receiving HMR or RMMR through the documented HbA1c and renal function (0). It was recently estimated that metformin was

not initiated in nearly 50% of patients with T2DM.²²⁶ Although the reason for the suboptimal prescribing were not defined clearly, it may be associated with the fear of precipitating LA, especially in patients with other underlying medical conditions.

Approximately 75% of the reported LA cases associated with metformin from the TGA (Chapter 4) were found to have other underlying condition(s) which might cause acidosis. In the study from RHH which investigated the LA cases (Chapter 5), all patients receiving metformin had other risk factor(s) associated with LA (either chronic or acute). It was difficult to identify the contribution of metformin in these cases as it occurred in the presence of other complications i.e. renal impairment).

It has been summarised that the drug does not accumulate in metformin-treated patients with mild to moderate CKD (eGFR 30-60 ml/min per 1.73m²) without increased risk of LA.²²⁵ The metformin dosage recommendation for patients with CKD in the PI are increasingly being disregarded.^{91, 140, 164, 294, 298} The European Medicines Agency has begun a review on all the PI of metformin-containing medicines to look at recommendations on how they were used with moderate renal impairment in early 2016. This action is in response to a request from the Dutch medicines agency (the Medicines Evaluation Board), which suggested that the evidence may not justify contraindicating metformin in patients with moderate reduction of kidney function.²⁹⁹ Mostly recently, the FDA announced that metformin can be used safely in patients with mild and moderate kidney impairment (but not recommending to start metformin in patients with an eGFR between 30-45 ml/min per 1.73m²), and the drug is still contraindicated in those with an eGFR below 30 ml/min per 1.73m².²⁷⁹ Metformin should no longer be contraindicated in patients with moderate renal impairment, and all the patients with an eGFR > 30 ml/min per 1.73m² or CrCl >30 ml/min should be safe when treated with this drug.

It has been reported that metformin was tolerated in patients with eGFR < 30 ml/min per 1.73m².²²³ Due to the lack of supportive evidence, the usage of metformin in patients with severe CKD (eGFR < 30ml/min per 1.73m²) is still not recommended. A recent study conducted in Taiwan,²⁸³ which included T2DM patients with advanced CKD (SCr > 530 µmol/L or stage 5 CKD), reported that the all-cause mortality was higher in metformin users compared to non-users. The authors suggested that metformin should be withdrawn in patients with stage 5 CKD. But the results from this study did not show that metformin was a significant risk factor for metabolic acidosis (including LA and other forms of metabolic acidosis). Also, the study did not report the causes of mortality; and the patients included (stage 5 CKD) had a short duration of diabetes (< 6 years), which may be suggestive of aggressive kidney disease.³⁰⁰

It is known that the risk of AKI is higher in patients with CKD.³⁰¹ AKI is one of the most common acute conditions co-existing in LA cases in metformin-treated patients. However, it is not generally clear whether metformin caused LA due to the drug accumulation in AKI, or if, LA was caused by the AKI (accompanied by dehydration, sepsis/infection) in metformin-treated patients. As there is limited evidence of the safe use of metformin in patients with severe CKD or those with risk of AKI, the drug should only be used in patients with stable renal condition, and further investigation in this population is required.

Although lactate levels had been mostly documented in case reports/ series of MALA, the levels are not commonly being measured in general practice. Several pathways have been suggested that metformin increases lactate production; however, the exact mechanism has not yet been established in patients with T2DM. The estimation of the incidence of MALA using the reports from TGA (Chapter 4) was 2.3 per 100,000 patient-years between 1997 and 2011. As the results showed in the review of lactate levels in metformin users (Chapter 6), including patients with contraindications (listed in the PI) to its use, the lactate levels did increase in metformin-treated patients. But the effect was modest; the reported lactate levels mostly

remained in the normal range. There was an observation of increasing number of lactate tests being performed in metformin-treated patients;²⁸⁸ however, it is also not clear regarding the clinical value of chronically monitoring lactate levels in metformin users. So far, most evidence indicates that metformin confers little if any risk of LA. The majority of LA cases reported in patients who were acutely unwell, or who had decreased tissue perfusion and shock (hypotension, sepsis, etc.).^{224, 287} If the lactate levels dramatically increase in acute conditions due to other reasons, then chronic measurement would not be useful in pre-empting this sudden medical illness.

Plasma metformin levels, are also not routinely measured in daily practice. The metformin concentration was not measured in the studies containing in this thesis. But the levels have been reported in studies elsewhere with the investigation for the reasons of so-called “MALA” cases. Whether it is useful to monitor metformin plasma concentration is not clear. As the results have varied between studies, there was no relationship established between metformin plasma concentrations and lactate levels.^{74, 302} It has been suggested that metformin plasma levels were generally measured many hours after admission.³⁰³ The patient’s metabolic status (i.e., the presence or the absence of lactic acidosis) may have changed during the time delay, even when metformin accumulation persisted.³⁰³ If the metformin concentration is a time-dependent valuable, which could be practically difficult to report, the plasma metformin measurement may not have much value in predicting or minimising LA.

In the latest systematic review and meta-analysis of 179 trials and 25 observational studies, the authors concluded that metformin should remain a first-line therapy for the treatment of T2DM.²⁵ They evaluated the comparative effectiveness and safety of monotherapy among antidiabetic medications, including thiazolidinediones, metformin, sulfonylureas, DPP-4 inhibitors, sodium–glucose co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, as well as selected metformin-based combinations. The review summarised that

metformin could be used for long-term treatment with beneficial effects on HbA1c and weight, without causing severe adverse effects. In addition, metformin was not associated with increased risk for LA.

The studies included in this thesis were all of retrospective design. Due to ethical issues and the very low incidence of MALA, it was not possible or practical to design a prospective study initiating/ continuing metformin treatment in patients with conditions listed as “contraindications” in the PI, which has strict restrictions for prescribing metformin in such a population. However, to obtain the information of inappropriate usage of metformin and the LA cases, the retrospective design enabled evidence as such to be established. The retrospective nature of the study could have rendered some of the data incomplete. The diagnosis of LA was based on the lab results or the documentation from the databases. Lastly, this thesis did not include information on metformin overdose, as the aim was to improve the safe use of the medication when taken in therapeutic dosages. Although LA has been reported in metformin overdose, it was not commonly found in metformin-treated patients.

In summary, metformin is generally safe to use in most patients with T2DM. The findings in this thesis support the loosening of cautions when using metformin. The “contraindications” listed in the official metformin PI are hindering the usage of this drug.¹³⁶ The recommendations regarding the usage of metformin in AMH have been modified over the last few years, with the level of restriction being lowered. The recommendations in the official PI of metformin are inconsistent with clinical guidelines. It is time to update the PI of metformin, to provide a clearer guidance for practitioners when prescribing the drug. With individualised risk-benefit assessment, unless it causes side effects or there is a high risk of LA, metformin therapy should not be excluded in patients with T2DM. Metformin could be used with caution in patients with stable medical conditions, which are including those conditions listed as contraindications in the official metformin PI. Very severe renal

impairment (CKD stage 5) would be the only absolute contraindication for the use of metformin. For patients with CKD, renal function should be assessed regularly. The drug should be ceased in patients who develop GI symptoms (including nausea, vomiting) or dehydration.²⁸⁷ It would be necessary to identify the reason for GI symptoms or dehydration before re-introducing metformin. Unless the contribution of metformin can be ruled out as a potential cause of LA, metformin should not be reintroduced in patients who have had LA, especially in those with complications. It is important to ensure the safe use of metformin in all patients to enjoy the benefits of this old drug.

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